Paediatric Gastroenterology, Hepatology and Nutrition

Shared Care Guideline

Thiopurine treatment for paediatric gastroenterology and hepatology patients

1. Scope

Prescribing and monitoring of thiopurine treatment of Paediatric gastroenterology and hepatology patients by general practitioners and/or general paediatricians.

2. Aim

To provide Shared Care Guidance on the prescribing and monitoring of thiopurine therapy in paediatric gastroenterology and hepatology patients.

3. Introduction

Thiopurines (azathioprine and 6-mercaptopurine) are immuno-modulatory agents used to induce and maintain remission in inflammatory bowel disease (IBD) and auto-immune hepatitis.

Azathioprine is non-enzymatically metabolised to mercaptopurine. Mercaptopurine is converted intracellularly to a ribonucleotide, which functions as a purine antagonist. Ultimately, the synthesis of RNA and DNA is inhibited and by this mechanism exhibits its immunosuppressive effect.

4. Abbreviations

- ALT alanine transaminase
- AST aspartate transaminase
- GP general practitioner
- IBD inflammatory bowel disease
- TPMT thiopurine methyltransferase
- VZV varicella zoster virus

5. Dose and Administration

- Azathioprine (CHILD 2-18 years): 2.5mg/kg once daily taken with or after food

- 6-mercaptopurine (CHILD 2-18 years): 1-1.5mg/kg ONCE daily (initial max. 50mg; may be increased to 75mg once daily) taken with or after food
- Therapeutic effect is usually evident after several weeks up to 3-6 months.
- Patients with a low TPMT will be started on half the normal dose. This will then be titrated according to response. **See 'Cautions' section below.**

6. Adverse Effects

Very common (≥ 1 in 10)

- Bone marrow suppression, leucopenia and therefore increased risk of infection (healthcare professional review is advised if temperature > 38°C and not responding to paracetamol for 24 hours)
- Nausea, vomiting, anorexia and abdominal discomfort

Common (≥ 1 in 100 and < 1 in 10)

- Thrombocytopenia

Uncommon (≥ 1 in 1000 and < 1 in 100)

- Anaemia
- Pancreatitis
- Cholestasis and degeneration of liver function tests (including hepatic necrosis)
- Hypersensitivity reactions (fever, rigors, rash, myalgia, arthralgia, hypotension, dizziness)

Rare (≥ 1 in 10000 and < 1 in 1000)

- Neoplasms – significantly skin cancer and lymphoma
- Alopecia
- Photosensitivity

See BNFc Section 8.2.1 or the Summary of Product Characteristics (SPC) (www.medicines.org.uk) for further information.

7. Cautions

- Due to potential adverse effects with thiopurines, patients need to be adequately monitored for its effects throughout the duration of treatment. **See 'Monitoring Standards' section.**
  The patient should be advised to report any signs of bone marrow suppression or hypersensitivity (i.e. infection, fever, chills, cough, unexplained bruising or bleeding, fatigue, hypotension, myalgia, dizziness) to their GP or general

paediatrician or paediatric gastroenterology team. Family will be provided with Medicines for Children – Azathioprine for inflammatory bowel disease – patient information leaflet.

- Prior to commencing thiopruine therapy the prescriber should check the patient's varicella zoster virus (VZV) immunity despite a positive history of previous exposure.
- The prescriber should also document if the patient has any history of VZV.
- Patients who have no history of exposure should be advised to avoid contact with individuals with chickenpox or herpes zoster. If the patient is exposed to VZV, this should be reported to the GP or hospital specialist for immediate action
- Patients who have no immunity should be vaccinated prior to commencing Thiopurine treatment if clinically appropriate.
- Patients with no immunity should be provided with a letter to act as emergency plan in the event of exposure – **see section 11**
- Cold sores should be reported to the GP as topical and/or oral antiviral therapy may be required.
- Patients may have an inherited deficiency of the enzyme thiopurine methyltransferase (TPMT) which will make them unusually sensitive to the myelosuppressive effect. Patients will have TPMT levels checked prior to starting thiopurine treatment, with results included in clinic letters. The TPMT level will define the patient as either deficient (< 10mU/L), low (20 - 67mU/L), normal (68 - 150mU/L) or high >150mU/L). Patients with a low TPMT level will start on half of the normal dose and titrated to tolerance. Treatment may be reconsidered in those who are deficient. Those with a high activity will metabolise the thiopurine more quickly and therefore the therapeutic effect and hepatotoxicity (due to the inactive metabolites) will be closely monitored.
- Careful assessment of risk versus benefit should be carried out before use during pregnancy and breastfeeding. A discussion should be carried out between the patient and the hospital specialist team at the time of pregnancy.
- Exposure to sunlight and UV light should be limited and patients should wear protective clothing and use a sunscreen with a high protection factor (30-50) to minimise the risk of skin cancer and photosensitivity.

8. Contraindications

- Hypersensitivity to azathioprine, 6-mercaptopurine (metabolite of azathioprine) or to any of the excipients
- Severe infections
- Severely impaired hepatic or bone-marrow function
- Pancreatitis
- Any live vaccine e.g. BCG, smallpox, yellow fever
- Pregnancy unless the benefits outweigh the risks

9. Drug Interactions

- **Allopurinol** – decreased metabolism of thiopurines. The dose of azathioprine/mercaptopurine must be reduced to a quarter of the original dose
- **Immunosuppresives (ciclosporin/tacrolimus)** – increased risk of immunosuppresion
- **ACE-inhibitors, co-trimoxazole / trimethoprim, cimetidine or indomethacin** - increased risk of myelosuppression
- **Warfarin** - Anticoagulant effect of warfarin possibly reduced by thiopurines.
- **Aminosalicylic acid derivatives (olsalazine, mesalazine and sulphasalazine)** - increased myelosuppressive effect of azathioprine, as a result of inhibition of its hepatic metabolism.

See BNFc section 8.2.1 and BNFc Appendix 1 for further details on interactions.

10. Monitoring Standards

Due to geographical location of patients in relation to CUH the gastro team requests that during the first four weeks bloods are organized by the GP. The paediatric gastroenterology will provide advice on dosing and further blood tests until dose is stable.

All blood test results are to be faxed promptly to the paediatric gastroenterology team regardless if result is abnormal or not.

Monitoring During Therapy to be undertake by GP	
• **Differential FBC** • **U&E's** • **LFT's including GGT**	Month 1: Weekly (until 4 weeks on a stable dose) Month 2: Fortnightly Month 3: Monthly Month 4 onwards: At least every 3 months
• **CRP** • **ESR**	With above bloods at week 1, 6, and 12 Thereafter: At least every 3 months These results will be reviewed periodically by the paediatric gastroenterology team when faxed.
	More frequent blood tests will be needed if: • if high dosages are used • if renal function is impaired • if hepatic function is mildly to moderately impaired • if bone marrow function is mildly to moderately impaired in patients with hypersplensim The paediatric gastroenterology team will provide advice on the tests needed and frequency.

• **Amylase**	If the patient complains of central abdominal pain/has clinical signs of pancreatitis amylase blood test to be organised and urgent advice sought from the paediatric gastroenterology team.

11. Actions to take in the event of abnormal test results/symptoms

TEST	ACTION
Abnormal Blood Test Results	
White cell count < 2.5 x 10^9/L	**Stop azathioprine and discuss with paediatric gastroenterology team immediately**
Haemoglobin <100 g/L **Platelets <150 x 10^9**	• **Contact the paediatric gastroenterology team if less than baseline**
Neutrophils **< 1.0 x 10^9/L** **1 – 1.5 x 10^9/L**	• **Stop Azathioprine/6-mercaptopurine and contact the paediatric gastroenterology team.** • **Re-check in one week and contact paediatric gastroenterology team for guidance to restart.**
MCV > 105 fl	• **Check B12, folic acid and thyroid stimulating hormone (TSH). Treat as appropriate and discuss with the paediatric gastroenterology team.**
Abnormal LFT Results	
>2 fold rise in AST, ALT (from upper limit of reference range)	• **Repeat LFT's in 1 month.**
>3 fold rise in AST, ALT(from upper limit of reference range)	• **Stop Azathioprine/6-mercaptopurine and contact the paediatric gastroenterology team.**
Abnormal Symptoms	
Severe or persistent infections, fever, chills and/ or persistent sore throat	• **Stop Azathioprine/6-mercaptopurine and check FBC.** • **If FBC is <u>abnormal</u> contact the paediatric gastroenterology team.** • **If FBC is <u>normal</u>, wait until infection resolved and restart at original dose.**

Abnormal bruising or bleeding (bleeding that does not stop with applied pressure or bruising that is unexplained)	• **Stop Azathioprine/6-mercaptopurineand contact the paediatric gastroenterology team.**
Presence of cold sores	• **Treat with topical aciclovir** • **Treat with a course of oral aciclovir if not responding to topical in 2 days.**
Varicella **Shingles**	• **If the patient does not have immunity, check VZV IgM – ASAP and administer IVIG with 72 hours of exposure** • **Contact the paediatric gastroenterology team with ANY concerns** • **Oral acyclovir and supportive treatment**

12. Shared Care

Sharing of care depends on communication between the specialist, GP and the patient or their parent/carer. 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. The doctor/healthcare professional who prescribes the medication has the clinical responsibility for the drug and the consequences of its use.

13. Shared Care Responsibilities

Aspects of care for which paediatric gastroenterology team are responsible for:

1) Initiate treatment and prescribe the first month of treatment
2) At point of initiating treatment check for drug interactions and contraindications
3) Undertake baseline bloods including differential FBC, U & E's, LFTs including GGT, TMPT phenotype, varicella status, EBV, ESR, CRP, Hep B and C
4) Review the first four weekly bloods, if not undertaken at Addenbrookes request local team fax them to paediatric IBD team.
5) Counsel the patient/carer on the potential benefits and side effects of treatment and provide the patient information leaflet. Patient will be explained the principles of shared care during the consultation.
6) Send a letter to the GP/general paediatrician requesting shared care for the patient. This letter will include initial dosing, TPMT status, contact details and a blood test timetable.
7) Assess the patients regularly in clinic throughout treatment and update local teams.
8) To inform the GP/general paediatrician after each clinic attendance if there is any change to treatment or monitoring.

9) Inform GP/general paediatrician of patients who do not attend clinic appointments.
10) To provide any advice to the local team / patient /carer when requested. Monitoring active metabolites twice a year

General Practitioner/ General Paediatrician

1) Agreement to shared care guideline by the GP/general paediatrician.
2) Fax blood test results to the paediatric gastroenterology team.
3) **Prescribe the drug treatment as described.**
4) **Monitor disease progression, and drug effects as advised by the paediatric gastroenterology team.**
5) Ensure more frequent blood monitoring is conducted if any abnormal blood results have been reported.
6) **Request advice from the paediatric gastroenterology team when necessary.**
7) Provision of pneumococcal type and annual influenza vaccination (not live version). Prevenar is given for patients < 2 years of age, Pneumovax for patients > 2 years of age.

Patient or parent/carer

1) Report to the paediatric gastroenterology team or GP if they do not have a clear understanding of their treatment.
2) Patients must take the recommended dose.
3) Patients must attend their scheduled clinic and blood test appointments.
4) Must inform relevant healthcare professionals (GP/practice nurse/ school nurse/ dentist/community pharmacist/ complimentary therapist) that they are receiving thiopurine treatment.
5) Report any adverse effects to the paediatric gastroenterology team or GP.

14. Contact numbers for advice and support

Specialist	Post	Telephone
Mary Brennan	Paediatric Gastroenterology Clinical Nurse Specialist	01223 274757
Kate Wakefield	Paediatric Gastroenterology pharmacist	01223 254417
Dr Robert Heuschkel	Consultant Paediatric Gastroenterologist	Secretary - 01223 274827
Dr Franco Torrente	Consultant Paediatric Gastroenterologist	Secretary - 01223 349483
Paediatric IBD helpline/email		01223 274757 paediatricibd@addenbrookes.nhs.uk
Out of Hours	Paediatric registrar on call via switchboard	01223 245151 – request paediatric on call registrar is bleeped

Fax number		01223 596367

15. Monitoring compliance with and the effectiveness of this document

Compliance of the document will be evaluated at clinic visits and annual review by reviewing medical notes and available blood test results. It will also be discussed at clinical meetings.

A regular audit of blood test monitoring will also be carried out to ensure that practice is both safe and practical.

Any incident reports relating to the guideline will be discussed at the paediatric gastroenterology clinical governance meetings.

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Paediatric Gastroenterology, Hepatology and Nutrition

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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.