Shared Care Guideline

Thiopurine treatment for paediatric gastroenterology and hepatology patients

Executive Summary

Key information given to patients prior to commencing thiopurine:
Most common side effects:
- Slightly increased risk of infection hence blood tests are important to ensure white cell count is not too low.
- Feeling sick and/or being sick, to reduce the risk of this side effect please give the patient the thiopurine in the evening (before bed) with a snack – please avoid dairy products.

Important information:
- Factor 30-50 sunscreen is advised to be worn from end of March to end of October. End of October to March SPF 15 is encouraged.
- Live vaccines must not be given – please see letter re: vaccinations. We encourage children on thiopurines to be vaccinated in line with the National Vaccination Programme. In addition to this we encourage that the patient has the Pneumococcal and annual flu vaccine (information in the Shared care guideline for healthcare professionals).
- If the patient has a temperature of 38 or above and not responding to paracetamol or continues for more than 24 hours, their carer should seek advice from a healthcare professional.
- If the patient experiences central abdominal pain or is vomiting – we have advised a review by a healthcare professional is sought as checking amylase and Lipase is important to exclude pancreatitis.
- Before the patient is started on a thiopurine their chicken pox antibodies will be checked by CUH and the results communicated to the GP. If they DO NOT have immunity and are in direct contact with chicken pox or shingles, they should be prescribed an attenuated dose of aciclovir within 7 days of exposure as per the BNF for children. The GP can contact the duty virologist at CUH for further advice (Addenbrooke’s via contact centre – 01223 245151).
- Blood tests must be taken according to the timetable. The patient’s carers have been advised that should blood tests should not be missed but if they are please get them done as soon as possible.
- For the first 4 weeks the review and feedback of blood tests will be the responsibility of the CUH team.
- The GP should please discuss with the family how they will get feedback of blood test results if not being done at CUH following the first 4 weeks.
- If the blood tests are not been undertaken at CUH please give the family a copy to bring to the patient’s appointment.

Information provided:
- Medicines for children Azathioprine information sheet
- Shared care guideline for health care professionals

Support / Advice:
- Contact paediatric IBD help line on 01223 274757 or email add-tr.paediatricibd@nhs.net – This is not an emergency contact out of hours (after 16:00 – 08:00, not covered over weekend or bank holidays) please contact the contact centre on 01223 245151 and ask to bleep paediatric registrar on call.
- The responsibilities of the hospital specialist, GP and patient for this Shared Care Guideline can be found within this document here.
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. Further information about the general responsibilities of the hospital specialist and GP can be found here.

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

4. **Abbreviations**
   ALT alanine transaminase
   AST aspartate transaminase
   GP general practitioner
   IBD inflammatory bowel disease
   TPMT thiopurine methyltransferase
   VZV varicella zoster virus
   CUH Cambridge University Hospitals NHS Foundation Trust

5. **Dose and Administration**
   - Azathioprine (CHILD 2-18 years): 2.5mg/kg once daily taken with or after food
   - 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 a lower dose than normal – usually half the dose. This will then be titrated according to response. See ‘Cautions’ section below.

Further information can be found in the Summary of Product Characteristics (www.medicines.org.uk).
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

Further information can be found in the Summary of Product Characteristics (www.medicines.org.uk).

7. Cautions

- The patient should be advised to report any signs of bone marrow suppression or hypersensitivity (ie 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 thiopurine therapy the prescriber at CUH should check the patient’s varicella zoster virus (VZV) immunity despite a positive history of previous exposure and document if the patient has any history of VZV.
- 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.
- Patients who have no history of exposure will 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 and treatment commenced within 7 days.
- 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 by the CUH prescriber 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.

Further information can be found in the Summary of Product Characteristics (www.medicines.org.uk).

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

Further information can be found in the Summary of Product Characteristics (www.medicines.org.uk).

9. Interactions
- Allopurinol – decreased metabolism of thiopurines. The dose of azathioprine/mercaptopurine must be reduced to a quarter of the original dose
- Immunosuppressives (cyclosporin/tacrolimus) – increased risk of immunosuppression
- ACE-inhibitors, co-trimoxazole/trimethoprim, cimetidine or indomethacin – increased risk of myelosuppression
- Warfarin – Anticoagulant effect of warfarin possibly reduced by thiopurines. Monitor INR.
- Aminosalicylic acid derivatives (olsalazine, mesalazine and sulphasalazine) – increased myelosuppressive effect of azathioprine.
- Live vaccines – increased risk of the generalised infection.

Please note that the above list is NOT exhaustive. Before the patient starts any new medicine, they have been advised to check with the GP/prescriber.

Further information can be found in the Summary of Product Characteristics (www.medicines.org.uk).
10. Monitoring Standards & Actions to take in the event of abnormal test results/symptoms

Unless there are exceptional circumstances or prior arrangements in place, for the first 4 weeks of treatment bloods will be taken in CUH.

Following this the CUH team will provide advice on dosing and further blood tests until the dose is stable.

**Monitoring during therapy to be undertaken by GP**

<table>
<thead>
<tr>
<th>Test</th>
<th>Month 1: Weekly (until 4 weeks on a stable dose)</th>
<th>Month 2: Fortnightly</th>
<th>Month 3: Monthly</th>
<th>Month 4 onwards: At least every 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Differential FBC, U&amp;Es and LFTs including GGT</strong></td>
<td></td>
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<tr>
<td><strong>CRP and ESR</strong></td>
<td>With above bloods at week 1, 6, and 12</td>
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<td></td>
<td>Thereafter: At least every 3 months</td>
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<tr>
<td></td>
<td>These results will be reviewed periodically by the paediatric gastroenterology team when emailed.</td>
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</tbody>
</table>

More frequent blood tests will be needed if:
- high dosages are used
- renal function is impaired
- hepatic function is mildly to moderately impaired
- bone marrow function is mildly to moderately impaired
- in patients with hypersplenism

The paediatric gastroenterology team will provide advice on the tests needed and frequency.

**Amylase and Lipase**

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.

**Action to take in the event of abnormal test results/ symptoms**

<table>
<thead>
<tr>
<th>TEST</th>
<th>ACTION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Abnormal Blood Test Results</strong></td>
<td></td>
</tr>
<tr>
<td>White cell count &lt; 2.5 x 10^9/L</td>
<td>Stop azathioprine/mercaptopurine and discuss with paediatric gastroenterology team immediately</td>
</tr>
<tr>
<td>Haemoglobin &lt;100 g/L</td>
<td>Stop azathioprine/mercaptopurine and contact the paediatric gastroenterology team</td>
</tr>
<tr>
<td>Platelets &lt;150 x 10^9</td>
<td>Stop azathioprine/mercaptopurine and contact the paediatric gastroenterology team</td>
</tr>
<tr>
<td>Neutrophils a) &lt; 1.0 x 10^9/L</td>
<td>a) Stop Azathioprine/ mercaptopurine and contact the paediatric gastroenterology team.</td>
</tr>
<tr>
<td>b) 1 – 1.5 x 10^9/L</td>
<td>b) Re-check in one week and contact paediatric gastroenterology team for guidance to restart.</td>
</tr>
</tbody>
</table>
**Lymphocytes < 0.5**
Stop Azathioprine/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

<table>
<thead>
<tr>
<th>Condition</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;2 fold rise in AST, ALT (from upper limit of reference range)</td>
<td>Repeat LFTs in 1 month.</td>
</tr>
<tr>
<td>&gt;3 fold rise in AST, ALT (from upper limit of reference range)</td>
<td>Stop Azathioprine/mercaptopurine and contact the paediatric gastroenterology team.</td>
</tr>
</tbody>
</table>

### Abnormal Symptoms

<table>
<thead>
<tr>
<th>Condition</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe or persistent infections, fever, chills and/or persistent sore throat</td>
<td>Stop Azathioprine/mercaptopurine and check FBC. If FBC is abnormal contact the paediatric gastroenterology team. If FBC is normal, wait until infection resolved and restart at original dose.</td>
</tr>
<tr>
<td>Abnormal bruising or bleeding (bleeding that does not stop with applied pressure or bruising that is unexplained)</td>
<td>Stop Azathioprine/mercaptopurine and contact the paediatric gastroenterology team.</td>
</tr>
<tr>
<td>Presence of cold sores</td>
<td>Treat with topical acyclovir as per BNF for children</td>
</tr>
<tr>
<td></td>
<td>Treat with a course of oral aciclovir if not responding to topical in 2 days as per BNF for children</td>
</tr>
<tr>
<td>Varicella/Shingles</td>
<td>If the patient does not have immunity, Prescribe Acyclovir attenuated dose 7 days after exposure for 7 days Contact the paediatric gastroenterology team with ANY concerns If the patient develops lesions – commence Oral Acyclovir immediately, advise family if no improvement in 24-48 hours admission to hospital for IV Acyclovir may be necessary.</td>
</tr>
</tbody>
</table>

### 11. Shared Care Responsibilities

Hospital specialist (CUH paediatric gastroenterology):
- Initiate treatment and prescribe the first month of treatment
- At point of initiating treatment check for drug interactions and contraindications
- Undertake baseline bloods including differential FBC, U&Es, LFTs including GGT, TMPT phenotype, varicella status, EBV, ESR, CRP, Hep B and C
- Organise bloods for the first 4 weeks of treatment
- Review the first four weekly bloods, if not undertaken at CUH request local team to email to paediatric IBD team at add-tr.paediatricibd@nhs.net
• 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.
• 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.
• Assess the patients regularly in clinic throughout treatment and update local teams.
• Monitoring active metabolites twice a year
• Inform the GP after each clinic attendance if there is any change to treatment or monitoring.
• Inform GP of patients who do not attend clinic appointments. The GP does not need to take
  any action as the hospital specialist will contact the family and take action in these situations.
• To provide any advice to the local team/patient/carer when requested.

General practitioner:
• Agreement to shared care guideline by the GP/ general paediatrician.
• Prescribe the drug treatment as described.
• Monitor disease progression, and drug effects as advised by the paediatric gastroenterology
  team.
• Monitor drug therapy as per section 10 above.
• After 4 weeks, if advice is required, email blood test results to the paediatric gastroenterology
  team.
• Request advice from the paediatric gastroenterology team when necessary.
• 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:
• Report to the paediatric gastroenterology team or GP if they do not have a clear understanding
  of their treatment.
• Patients must take the recommended dose.
• Patients must attend their scheduled clinic and blood test appointments.
• Must inform relevant healthcare professionals (GP/ practice nurse/ school nurse/ dentist/
  community pharmacist/ complimentary therapist) that they are receiving thiopurine treatment.
• Report any adverse effects to the paediatric gastroenterology team or GP.

12. Contact numbers for advice and support

<table>
<thead>
<tr>
<th>Specialist</th>
<th>Post</th>
<th>Telephone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mary Brennan</td>
<td>Paediatric Gastroenterology Clinical Nurse Specialist</td>
<td>01223 274757</td>
</tr>
<tr>
<td>Emma Williams</td>
<td>Paediatric Pharmacist</td>
<td>01223 254412</td>
</tr>
<tr>
<td>Dr Robert Heuschkel</td>
<td>Consultant Paediatric Gastroenterologist</td>
<td>Secretary - 01223 274827</td>
</tr>
<tr>
<td>Dr Franco Torrente</td>
<td>Consultant Paediatric Gastroenterologist</td>
<td>Secretary - 01223 349483</td>
</tr>
<tr>
<td>Paediatric IBD helpline/email</td>
<td></td>
<td>01223 274757 <a href="mailto:add-tr.paediatricibd@nhs.net">add-tr.paediatricibd@nhs.net</a></td>
</tr>
<tr>
<td>Out of Hours</td>
<td>Paediatric registrar on call via switchboard</td>
<td>01223 245151 – request paediatric on call registrar is bleeped</td>
</tr>
</tbody>
</table>
13. Equality and Diversity Statement
This document complies with the Cambridge University Hospitals NHS Foundation Trust service Equality and Diversity statement.

14. Disclaimer
It is your responsibility to check that this printed out copy is the most recent issue of this document.

15. Document Management

<table>
<thead>
<tr>
<th>Document ratification and history</th>
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<tr>
<td>Approved by:</td>
</tr>
<tr>
<td>Cambridge University Hospitals NHS Foundation Trust</td>
</tr>
<tr>
<td>Joint drug and therapeutics committee</td>
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<tr>
<td>Date approved: 23 February 2021</td>
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<tr>
<td>Submitted for ratification by:</td>
</tr>
<tr>
<td>Cambridgeshire and Peterborough Joint Prescribing Group</td>
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<td>Date ratified: 4 February 2021</td>
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<tr>
<td>Authors:</td>
</tr>
<tr>
<td>Emma Williams – Paediatric Pharmacist</td>
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<tr>
<td>Mary Brennan – Paediatric Gastroenterology Nurse Specialist</td>
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<td>Dr R Heuschkel – Consultant Paediatric Gastroenterologist</td>
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<tr>
<td>Dr F Torrente – Consultant Paediatric Gastroenterologist</td>
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<tr>
<td>Owning Provider Trust: Cambridge University Hospitals NHS Foundation Trust</td>
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<td>Version number: 3</td>
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<tr>
<td>Summary of changes to updated version</td>
</tr>
<tr>
<td>Guideline put into new format</td>
</tr>
<tr>
<td>Executive summary added</td>
</tr>
<tr>
<td>Minor amendments to section 7 to work cautions more clearly.</td>
</tr>
<tr>
<td>Introduction added to section 10 and table reformatted.</td>
</tr>
<tr>
<td>First 4 weeks of bloods to be taken at CUH (removed option of bloods locally).</td>
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<td>CUH document ID: 32276</td>
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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 for azathioprine and mercaptopurine.