Clinical Guideline

AZATHIOPRINE IN PAEDIATRIC INFLAMMATORY BOWEL DISEASE (IBD)

SETTING  Bristol Royal Hospital for Children
FOR STAFF  Medical and Nursing Staff
PATIENTS  Children with Inflammatory bowel disease

GUIDANCE

TABLE OF CONTENTS

Introduction
I. Azathioprine metabolism
II. Indications
III. Dose and administration
IV. Side effects
V. Cautions and drug interactions
VI. Contraindications
VII. Monitoring

Introduction

Azathioprine is an immuno-modulatory agent that is used in Paediatric Gastroenterology to maintain remission in patients with Ulcerative Colitis and Crohn’s Disease. This document incorporates national and international guidelines, as well as local practices where evidence is lacking.

I. Azathioprine metabolism

Azathioprine is a pro-drug, which is cleaved rapidly in the liver to 6-mercaptopurine (6-MP) and then metabolised to the active metabolite 6-thioguanine (6-TGN). Thiopurine Methyl Transferase (TPMT) converts 6-MP to 6-methyl-mercaptopurine (6-MMP) (see figure 1). Testing of TPMT activity helps in the identification of patients at risk of early profound myelosuppression and is recommended prior to treatment. Dose should be reduced in heterozygous patients with low TPMT activity. Thiopurines should not be used in children who are homozygous for TPMT polymorphisms or those with extremely low TPMT activity. Myelosuppression may still occur in the presence of normal TPMT activity, which also does not identify patients at risk for other toxic or allergic adverse events, and therefore regular monitoring of blood counts and liver tests are recommended in all cases (see section VII).

The actual values for enzyme activity are not reliable if red blood cells have been transfused to the patients within the previous 3 months.
II. Indications

A) Ulcerative colitis

Azathioprine is recommended to maintain remission after a single episode of acute severe ulcerative colitis regardless of disease extent. In left-sided and extensive ulcerative colitis with mild to moderate exacerbation, the use of oral Azathioprine is considered after two or more inflammatory exacerbations in 12 months that require treatment with systemic steroids or if remission is not maintained by aminosalicylates.

B) Crohn’s disease

Azathioprine is recommended for maintenance of steroid-free remission in Crohn’s disease in children at risk for poor disease outcome:

- deep colonic ulcerations on endoscopy
- persistent severe disease despite adequate induction therapy
- extensive (pan-enteric) disease
- marked growth retardation
- severe osteoporosis
- stricturing and penetrating disease at onset
- severe perianal disease

Azathioprine should also be considered if there are two or more inflammatory exacerbations in a 12 month period requiring corticosteroids or if the corticosteroid dose cannot be tapered.
Azathioprine can be considered to maintain remission after surgery in patients with adverse prognostic factors such as more than one resections or previously complicated or debilitating disease (eg abscess, fistulising or penetrating disease).

**III. Dose and administration**

Azathioprine is licensed for use in children 2-17 years.

In patients with normal TPMT activity the recommended azathioprine dose is 2-2.5 mg/kg of azathioprine in a single daily dose. Full thiopurine dose may be prescribed from the outset without the need for gradual dose increase. Dose reduction to half is usually necessary in patients who are heterozygous in the TPMT gene or with intermediate enzymatic activity.

The therapeutic effect of thiopurines may take up to 10 to 14 weeks after the start of treatment. Dosing may be further adjusted depending on clinical response and 6-thioguanine levels (see section VII).

**Oral preparations available:**
- 25mg and 50mg tablets
- 50mg in 5mL solution

**IV. Side effects**

1) **Bone marrow suppression** (see table 1)

Patients should be advised to report to GP, IBD nurse and/or hospital specialist clinician any signs of bone marrow suppression, such as fever, infection, unexplained bruising of bleeding. If bone marrow suppression is mild (WBC>2.5), reduce dose and repeat FBC to confirm improvement; if moderate (WBC 1.5-2.5) stop Azathioprine for 1 week, then consider restarting at lower dose with weekly FBC monitoring; if severe (WBC <1.5), withdraw treatment and if patient is pyrexial admit for IV broad spectrum antibiotics and consider use of granulocyte stimulating factor (G-CSF). Also review dose if there other signs of bone marrow suppression eg lymphocytes <0.5, platelets <150. Consider measuring thiopurine metabolites.

2) **Transaminitis**

Increased transaminases twice above the upper normal value can be transient or resolve after drug tapering or discontinuation. Withdrawal of the drug if >4 fold rise usually leads to resolution of the abnormalities and a liver biopsy is rarely required (see table 1). Consider measuring thiopurine metabolites. Consider other causes of abnormal LFT’s.
<table>
<thead>
<tr>
<th>Blood test results</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total WBC</td>
<td>2.5 – 4 x 10^9/L&lt;br&gt;Reduce dose and repeat FBC. Discuss with hospital team</td>
</tr>
<tr>
<td></td>
<td>1.5-2.5 x 10^9/L&lt;br&gt;Withhold drug and repeat in 1 week. Consider restarting at lower dose with weekly FBC monitoring after discussion with hospital team</td>
</tr>
<tr>
<td></td>
<td>&lt;1.5 x 10^9/L&lt;br&gt;Withdraw treatment. Discuss with hospital team</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>&lt;1.0 x 10^9/L&lt;br&gt;Repeat and discuss with hospital team</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>&lt;0.5 x 10^9/L&lt;br&gt;Repeat and discuss with hospital team if still low</td>
</tr>
<tr>
<td>Platelets</td>
<td>&lt;150 x 10^9/L&lt;br&gt;Repeat and discuss with hospital team</td>
</tr>
<tr>
<td>AST / ALT / ALP</td>
<td>&gt;2 fold rise&lt;br&gt;Repeat and if still high discuss with hospital team</td>
</tr>
<tr>
<td></td>
<td>&gt;4 fold rise&lt;br&gt;Withhold medication, repeat and discuss with hospital team</td>
</tr>
</tbody>
</table>

*Table 1. Abnormal blood results and action required in patients on treatment with Azathioprine.*

3) **Pancreatitis**

Pancreatitis may occur early (within the first six weeks) after introduction of thiopurines, is dose-independent and is most often a hypersensitivity reaction, occurring in 3-4% of patients. It usually requires discontinuation of the drug.

4) **Other dose-independent adverse reactions**

Gastrointestinal intolerance (5–8%), fever, flu-like symptoms, myalgia, arthralgia and rash (occurring in ~9%). A shift to 6-MP may be successful in ~50% of Azathioprine-intolerant patients, especially in myalgia or arthralgia but may also be effective in hepatotoxicity, gastrointestinal symptoms, flu-like illness, or rash.

5) **Malignancies**

Thiopurines have been associated with a 4–5 fold increased risk of non-melanoma skin cancers even before the age of 50 years. Patients should be reminded to have adequate sun protection and mole examination when necessary.

The relative risk of lymphoma is increased in IBD patients taking thiopurines when compared with the general population. The increased risk of lymphoma could be a result of the medications, the severity of the underlying disease, or a combination of the two. Care should be taken to avoid use of thiopurines during infection with Ebstein-Barr virus (EBV) due to the risk of EBV associated lymphomas.
In addition, a very rare fatal hepatosplenic T-cell lymphoma (HSTCL) has occurred in nearly 40 teenage and young adult patients with IBD, almost all male. About half of the patients had been treated with long-term thiopurines only and the other half with long-term thiopurines and anti-tumor necrosis factor antibody therapy.

It is important to emphasize that there remains a very low absolute risk of lymphoma for any given patient. For patients of all ages and genders, the risk of lymphoma needs to be weighed against the potential benefits of therapy.

V. Cautions and drug interactions

**ACE inhibitors:** Increased risk of leucopenia.

**Allopurinol:** increased toxicity. Reduce Azathioprine dose to 25% of original dose.

**Anticoagulants** (coumarins): possible reduced anticoagulant effect.

**Antibacterials** (co-trimoxazole & Trimethoprim): possible haematological toxicity increased.

**Phenytoin:** Azathioprine possibly reduces absorption of phenytoin.

**Clozapine:** avoid concomitant use – increased risk of agranulocytosis.

**Live vaccines:** patients should avoid live vaccines such as MMR, VZV, BCG, oral polio, oral typhoid and yellow fever whilst on immunosuppressive therapy.

**VZV contact:** Patients should avoid contact with people with active chickenpox or shingles and should report any such contact to their hospital specialist. For more information, please refer to the separate guideline on VZV in immunocompromised patients with IBD.

**Renal or hepatic insufficiency:** patients may need reduced doses and more frequent monitoring, as significant haematological impairment can occur.

**Pregnancy:** treatment should not generally be initiated during pregnancy. The use of the drug during pregnancy needs to be supervised in specialist units.

VI. Contraindications

1. TPMT deficiency
2. Severe infections
3. Severe hepatic or bone marrow function impairment
4. Pancreatitis
5. Hypersensitivity reaction to Azathioprine or Mercaptopurine
VII. Monitoring

**Pre-treatment:**

FBC, LFT’s, TPMT enzyme activity.

Vaccination status should be assessed in all children. An attempt should be made to immunize with live vaccines >6 weeks before starting immunosuppressive agents, but immunization should not delay necessary medications to control the disease.

**Subsequently:**

FBC, LFT’s at week 2, 4, 8, 12 and then 3 monthly thereafter.

Determination of thiopurine metabolites (6-TGN and 6-MMP) should be considered by the Paediatric Gastroenterology Consultant in patients with elevated ALT, cytopenia, or in suboptimal response and to monitor adherence (see table 2). In TPMT hypermetabolizers (i.e. having low 6-TGN and high 6MMP), split dose regimen or adding allopurinol together with a reduced thiopurine dose (25–33% of the original dose) can successfully restore the desired 6-TGN/6-MMP balance and clinical effectiveness. Allopurinol is not licensed for this indication in children and any decision regarding this should be made by the lead Paediatric Gastroenterology Consultant.

<table>
<thead>
<tr>
<th>6-TGN</th>
<th>6-MMP</th>
<th>Possible adverse event or finding</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (&lt;230)</td>
<td>Low–normal (&lt;5700)</td>
<td>--</td>
<td>Improve compliance or increase thiopurine dose as appropriate</td>
</tr>
<tr>
<td>Low or normal</td>
<td>High ≥ 5700</td>
<td>Hepatotoxicity and others</td>
<td>Preferred option is to try split dose regimen Or consider alternative</td>
</tr>
<tr>
<td>Normal 230-450</td>
<td>High &gt;5700</td>
<td>Normal LFT’s</td>
<td>Standard monitoring</td>
</tr>
<tr>
<td>Therapeutic (230–450)</td>
<td>Normal or high</td>
<td>Active disease</td>
<td>Consider changing treatment strategy</td>
</tr>
<tr>
<td>High levels &gt;450</td>
<td>normal</td>
<td>Myelosuppression</td>
<td>Consider dose reduction and repeat (between 450-550 can be tolerated without changes)</td>
</tr>
</tbody>
</table>

*Table 2. Thiopurine metabolite monitoring.*
REFERENCES

1. https://www.nice.org.uk/guidance/cg166
   NICE guidelines. Ulcerative colitis: management. Published June 2013
3. https://www.nice.org.uk/guidance/cg152
   NICE guidelines. Crohn’s disease: management. Published October 2012, last update May 2016
   British Society of Paediatric Gastroenterology, Hepatology and Nutrition (accessed 24/10/2018)
6. BNF for Children 2017-2018

Table A

<table>
<thead>
<tr>
<th>RELATED DOCUMENTS</th>
<th>AUTHORISING BODY</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Paediatric Gastroenterology Governance Group</td>
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| SAFETY           | Contact gastroenterology CNS on Ext 28226 / Bleep 3317 or gastroenterology SpR on Bleep 2351 or 2281. |