Overview of azathioprine and mercaptopurine use in inflammatory bowel disease

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INTRODUCTION

Thiopurines (ie, azathioprine [AZA] and mercaptopurine, also known as 6-mercaptopurine, [6-MP]) exert a glucocorticoid-sparing effect for patients with inflammatory bowel disease (IBD) who cannot maintain remission when glucocorticoids are tapered and withdrawn.

The pharmacology, dosing, laboratory monitoring, and adverse effects of thiopurines in the setting of IBD will be reviewed here. 6-MP metabolite monitoring, thiopurine-S-methyltransferase (TPMT) testing, and the indications and efficacy of AZA and 6-MP for patients with inflammatory bowel disease are presented separately.

- (See "Thiopurines: Pretreatment testing and approach to therapeutic drug monitoring for adults with inflammatory bowel disease".)
- (See "Management of moderate to severe ulcerative colitis in adults".)
- (See "Medical management of moderate to severe Crohn disease in adults".)

PHARMACOLOGY

Metabolism — Azathioprine is a prodrug that is quickly converted to 6-mercaptopurine via a nonenzymatic nucleophilic attack by sulfhydryl-containing compounds, such as glutathione,

present in red blood cells and other tissues. 6-MP is then metabolized in the liver and gut by one of three enzymes (figure 1) [1,2]:

- Thiopurine-S-methyltransferase (TPMT), which catalyzes the methylation of 6-MP to an inactive metabolite 6-methyl-mercaptopurine
- Xanthine oxidase, which catalyzes 6-MP to inactive thiourate
- Hypoxanthine-guanine-phosphoribosyltransferase, which converts 6-MP to active metabolite 6-thioguanine nucleotides

Absorption — The absorption of azathioprine (AZA) ranges between 16 to 50 percent in healthy subjects. Absorption may be reduced in patients with Crohn disease and ulcerative colitis due to increased intestinal motility during acute exacerbations [1,2].

Mechanism of action — Following absorption, 6-thioguanine nucleotides (6-TGN) exert their immunosuppressive effects by inhibition of purine and protein synthesis in lymphocytes [3-5]. The therapeutic effect of thiopurines has been associated with the level of active 6-TGN metabolites in patients with inflammatory bowel disease [6]. (See "Thiopurines: Pretreatment testing and approach to therapeutic drug monitoring for adults with inflammatory bowel disease", section on 'Therapeutic drug monitoring'.)

In addition, AZA and 6-MP inhibit the proliferation of T and B lymphocytes, leading to decreased production of cytotoxic T lymphocytes and plasma cells. They also lead to apoptosis of T-cells [7].

The molecular weight of 6-MP is 55 percent that of AZA, and 88 percent of AZA is converted to 6-MP. As a result, a conversion factor of 0.5 is used to convert a dose of AZA to 6-MP [1,8].

The mechanism of action of azathioprine is discussed in more detail separately. (See "Pharmacology and side effects of azathioprine when used in rheumatic diseases", section on 'Mechanism of action'.)

Timing of response — AZA and 6-MP are both slow-acting drugs. A therapeutic response is typically observed after three months of therapy but may take longer (ie, up to six months) in some patients.

Drug interactions — Two serious drug interactions with AZA or 6-MP are allopurinol and febuxostat, which slow the elimination of 6-MP by inhibiting xanthine oxidase. (See "Pharmacology and side effects of azathioprine when used in rheumatic diseases", section on 'Xanthine oxidase inhibitors'.)

Specific interactions may be determined using the Lexicomp drug interactions included in UpToDate. This tool can be accessed from the UpToDate online search page or through the individual drug information topics in the section on drug interactions. (See "Azathioprine: Drug information".)

DOSING AND MONITORING

Dosing strategies for azathioprine (AZA) and 6-MP include (1) empiric, gradual dosing or (2) dosing based on thiopurine-S-methyltransferase (TPMT) genotype or enzymatic activity (phenotype) testing.

Empiric dosing and laboratory monitoring — The authors use empiric, gradual dosing with target doses that are generally weight-based [9-11]. While TPMT testing is available, there remains a cost barrier to its use as a first-line test for many patients. In addition, the frequency of homozygous variants is low (about 1 in 300 patients), and polymorphisms in the TPMT gene and their effects are discussed elsewhere. The authors reserve TPMT testing for patients who experience treatment-related leukopenia or other adverse effects (eg, abnormal liver chemistries) after initiating low dose thiopurine (AZA or 6-MP 50 mg daily). While AZA and 6-MP are well-tolerated in many patients with IBD, laboratory monitoring does not always prevent bone marrow suppression or hepatotoxicity, which can be sudden in onset, even after a long duration of therapy [1]. Patients are instructed to report any new symptoms while on therapy.

- (See "Overview of pharmacogenomics", section on 'Thiopurines and polymorphisms in TPMT and NUDT15'.).
- (See "Thiopurines: Pretreatment testing and approach to therapeutic drug monitoring for adults with inflammatory bowel disease".)
- (See "Pharmacology and side effects of azathioprine when used in rheumatic diseases", section on 'Pharmacogenetics and azathioprine toxicity'.)

We initiate fixed, low dosing and adjust gradually as follows:

- **Week 1 to 4**: Start AZA (or 6-MP) at 50 mg once daily. Despite the difference in potency, it is acceptable to initiate either thiopurine at 50 mg once daily.

  Obtain weekly laboratory testing (ie, complete blood count [CBC], serum aminotransferases, total bilirubin, and amylase) [12].

- **Weeks 5 to 8:** If the patient is tolerating the drug, the white blood cell (WBC) count is >4000 cells/microL and the platelet count is ≥150,000/microL, increase the dose of AZA to

100 mg daily (6-MP 75 mg daily), provided that this dose is less than the maximum dose as determined by the patient's lean body weight, rather than the actual body weight (calculator 1 and calculator 2):

- AZA daily maximum dose is 2.5 mg/kg based on estimated lean body weight.
- 6-MP daily maximum dose is 1.5 mg/kg based on estimated lean body weight.

Obtain laboratory testing (ie, CBC, serum aminotransferases, total bilirubin, and amylase) every two weeks.

- **Weeks 9 to 12:** If the patient is tolerating the drug, the WBC count is >4000 cells/microL and the platelet count is ≥150,000/microL, AZA is further increased to 150 mg daily (6-MP increased to 100 mg daily) provided that this dose is less than the maximum dose as determined by the patient's lean body weight (as shown above).

  Obtain laboratory testing (ie, CBC, serum aminotransferases, total bilirubin, and amylase) every two weeks.

- **After 12 weeks:** After this stable maintenance dose is reached, obtain laboratory monitoring (ie, CBC, serum aminotransferases, total bilirubin, and amylase) at least every three months.

For the occasional patient who is not responding to therapy (eg, unable to taper glucocorticoids) and has not reached the maximum weight-based dose, a further increase in dose may be indicated. For example, the dose of 6-MP for a patient with a lean body weight of 85 kg would be gradually increased to a weight-based, maximum dose of 125 mg daily (approximately 1.5 mg/kg daily).

Laboratory testing is performed in two weeks following any dose escalation.

For additional drug prescribing information, please refer to the Lexicomp database and drug label information.

Dose adjustment for cytopenia — In patients who develop leukopenia (WBC ≤4000 cells/microL) or thrombocytopenia (platelet count <150,000/microL) during therapy, the AZA or 6-MP dose should be reduced by 50 percent or the drug should be discontinued. A repeat CBC should be checked within two weeks. If a 50 percent reduction in the dose is associated with persistent cytopenia, then AZA or 6-MP should be permanently discontinued [10] (see "Drug-induced neutropenia and agranulocytosis").

Some data suggest that other genetic variants such as nudix hydrolase-15 (NUDT15) are associated with increased risk of thiopurine-induced bone marrow suppression [13-15]. However, we do not routinely test for NUDT15 because the optimal clinical circumstances in which to perform testing are not well-defined. Genetic variants that affect the metabolism of thiopurines are discussed in more detail separately. (See "Overview of pharmacogenomics", section on 'Thiopurines and polymorphisms in TPMT and NUDT15' and 'Dosing based on TPMT enzyme testing' below.)

Abnormal liver chemistries — Mild hepatitis (transaminitis) is usually reversed by lowering the drug dose. In patients in whom the serum alanine or aspartate aminotransferase become elevated, therapy can be continued by reducing the dose of 6-MP or AZA by 33 to 50 percent, while following liver function every two weeks. If serum alanine or aspartate aminotransferase exceed more than two times the upper limit of normal, treatment with AZA/6-MP should be discontinued until they normalize, after which AZA/6-MP can be reintroduced at a lower dose.

Both 6-MP and AZA have been rarely associated with severe cholestatic jaundice, which may progress despite discontinuing therapy [16]. Thiopurines should be stopped (and not introduced) in patients with an elevated total bilirubin.

Macrocytosis — Patients who develop macrocytosis should be closely monitored with more frequent CBC (eg, initially every two weeks for a month) after other major causes of macrocytosis have been excluded, including vitamin B12 and folate deficiency. Stable, mild macrocytosis in the absence of vitamin deficiency is a potential side effect that is well-tolerated and does not require discontinuation of medication. (See "Pharmacology and side effects of azathioprine when used in rheumatic diseases", section on 'Dose titration and monitoring'.)

Dosing based on TPMT enzyme testing — Some clinicians base dosing on TPMT enzyme testing. Initial genotype or phenotype testing for TPMT is suggested but not required by the United States Food and Drug Administration prior to use. If TPMT genotyping is normal, a gradual increase of the dose as discussed above is not necessary and the drug can be started at full (ie, goal) dose (maximum dose: AZA 2.5 mg/kg daily or 6-MP 1.5 mg/kg daily). (See "Thiopurines: Pretreatment testing and approach to therapeutic drug monitoring for adults with inflammatory bowel disease".)

METABOLITE TESTING

Toxicity of azathioprine and 6-MP is related to their metabolites (6-TG and 6-MMP in particular) (figure 1). The relative accumulation of these metabolites depends upon genetic

polymorphism of the individual enzymes, and this is discussed separately. (See "Thiopurines: Pretreatment testing and approach to therapeutic drug monitoring for adults with inflammatory bowel disease".)

DURATION OF TREATMENT

Patients who are in clinical remission and then discontinue thiopurines have a high rate of relapse, and most studies suggest that thiopurine monotherapy should be continued for the long-term (ranging from one to five years) to lower the risk of relapse [17-20].

If it is decided that thiopurine therapy will be discontinued, there is no need for a taper as it is unknown if this reduces the risk of disease relapse.

ADVERSE EFFECTS

Frequency of adverse effects — Adverse effects occur in approximately 10 percent of patients with inflammatory bowel disease treated with azathioprine (AZA) and 6-mercaptopurine (6-MP) and most often occur during the first month [11]. Approximately 10 to 20 percent are severe enough to stop treatment [21,22]. (See "Pharmacology and side effects of azathioprine when used in rheumatic diseases".)

Switching from 6-MP to AZA or vice versa does not reduce the risk of side-effects. Patients who develop hypersensitivity reactions to either AZA or 6-MP should not receive either of these drugs, because those who have hypersensitivity reactions to one drug are at increased risk upon exposure to the other [23].

There is no evidence to support a dose reduction in patients in remission in order to prevent long-term side effects. Furthermore, a dose reduction may put the patient at risk for relapse. Thus, once therapy is tolerated and remission is maintained, there does not appear to be a compelling reason to reduce the dose.

Side effects and adverse events — The side effects of AZA and 6-MP include dose-dependent side effects (eg, bone marrow suppression and hepatotoxicity) and dose-independent side effects (eg, nausea, pancreatitis, infection, malignancy).

The most commonly encountered side effects are anorexia, nausea, and vomiting, especially if the dose is increased too rapidly [24]. Dyspeptic symptoms can be minimized by taking the drug with meals. Adverse effects including are discussed in more detail separately. (See

"Pharmacology and side effects of azathioprine when used in rheumatic diseases", section on 'Adverse effects'.)

Malignancy

Lymphoma — There is some evidence suggesting a small increased risk of malignancy, particularly lymphoma, in patients with IBD who are treated with thiopurines [25-29]. The magnitude of the risk of developing lymphoma is low when viewed in absolute terms (ie, less than one case per 1000 person years) [28]. In a large cohort study of over 189,000 patients with IBD, the risk of lymphoma was increased in patients exposed to thiopurine monotherapy (aHR 2.6, 95% CI 1.96-3.44) compared with patients who were not exposed to thiopurines or anti-tumor necrosis factor (TNF) agents during a median follow-up of 6.7 years [28]. A meta-analysis of six studies estimated that the risk of lymphoma in patients with IBD treated with AZA or 6-MP was increased fourfold compared with the general population [30]. The risk of lymphoma with thiopurine use appears to increase gradually over successive years with a reduction in risk with discontinuation of therapy [31].

Whether the increased risk of lymphoma is due to the medications alone or the combination of medications and the underlying IBD is unclear [32]. Alimentary tract lymphoma has also been described in the absence of treatment with AZA or 6-MP [33,34].

Hepatosplenic T cell lymphoma — Long-term thiopurine use (more than two years) appears to be a common denominator in cases of hepatosplenic T-cell lymphomas (HSTCL), and may be particularly important in young male patients [35,36]. The risk of HSTCL in patients on thiopurine monotherapy or in combination with anti-TNF antagonists is discussed separately. (See "Medical management of moderate to severe Crohn disease in adults", section on 'Hepatosplenic T-cell lymphoma'.)

Skin cancer — The use of AZA or 6-MP has been associated with an increased risk of nonmelanoma skin cancer. (See "Dermatologic and ocular manifestations of inflammatory bowel disease", section on 'Skin cancer'.)

Fertility — Limited studies suggest that azathioprine may be relatively safe with regard to effects on male fertility. Thiopurines have been widely used in organ transplantation and rheumatic disease, and further details regarding preconception counseling are discussed separately. (See "Fertility, pregnancy, and nursing in inflammatory bowel disease", section on 'Preconception counseling' and "Effects of antiinflammatory and immunosuppressive drugs on gonadal function and teratogenicity in men with rheumatic diseases".)

THIOPURINE USE DURING PREGNANCY

The use of azathioprine and 6-mercaptopurine in pregnancy and nursing is discussed separately. (See "Fertility, pregnancy, and nursing in inflammatory bowel disease".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Ulcerative colitis in adults" and "Society guideline links: Crohn disease in adults".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Ulcerative colitis in adults (The Basics)")
- Beyond the Basics topics (see "Patient education: Ulcerative colitis (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Pharmacology** – Azathioprine (AZA) is a prodrug that is quickly converted to 6-mercaptopurine (6-MP) via a nonenzymatic nucleophilic attack by sulfhydryl-containing compounds, such as glutathione, present in red blood cells and other tissues. 6-MP is then metabolized in the liver and gut by one of three enzymes: thiopurine-S-methyltransferase, which catalyzes the methylation of 6-MP to an inactive metabolite, 6-methyl-

mercaptopurine; xanthine oxidase, which catalyzes 6-MP to inactive thiourate; and hypoxanthine-guanine-phosphoribosyltransferase, which converts 6-MP to active metabolite 6-thioguanine nucleotides (figure 1). (See 'Pharmacology' above.)

- **Dosing and monitoring** – For empiric dosing, AZA is initiated at 50 mg and increased incrementally over 12 weeks to maximum dose of 2.5 mg/kg daily, based on estimated lean body weight (calculator 1 and calculator 2). The initial dose of 6-MP is 50 mg daily and is increased incrementally over 12 weeks to a maximum of 1.5 mg/kg daily, based on estimated lean body weight.

  The thiopurine dose is only increased if the patient is tolerating the drug, the white blood cell count is >4000 cells/microL, and the platelet count is ≥150,000/microL. The daily dose of thiopurine should not exceed the maximum dose as determined by the patient's lean body weight. (See 'Dosing and monitoring' above.)

- **Timing of response** – AZA and 6-MP are both slow-acting drugs. A therapeutic response is typically observed after three months of therapy but may take longer (ie, up to six months) in some patients. (See 'Timing of response' above.)

- **Adverse effects** – Side effects occur in approximately 10 percent of patients with inflammatory bowel disease (IBD) who are treated with thiopurines and include dose-dependent side effects (eg, bone marrow suppression and hepatotoxicity) and dose-independent side effects (eg, nausea and pancreatitis). These patients are also at increased risk for infection and malignancy. (See 'Adverse effects' above.)

- **Fertility** – Limited studies suggest that azathioprine may be relatively safe with regard to effects on male fertility. Thiopurines have been widely used in organ transplantation and rheumatic disease, and further details regarding preconception counseling are discussed separately. (See "Fertility, pregnancy, and nursing in inflammatory bowel disease", section on 'Preconception counseling' and "Effects of antiinflammatory and immunosuppressive drugs on gonadal function and teratogenicity in men with rheumatic diseases".)

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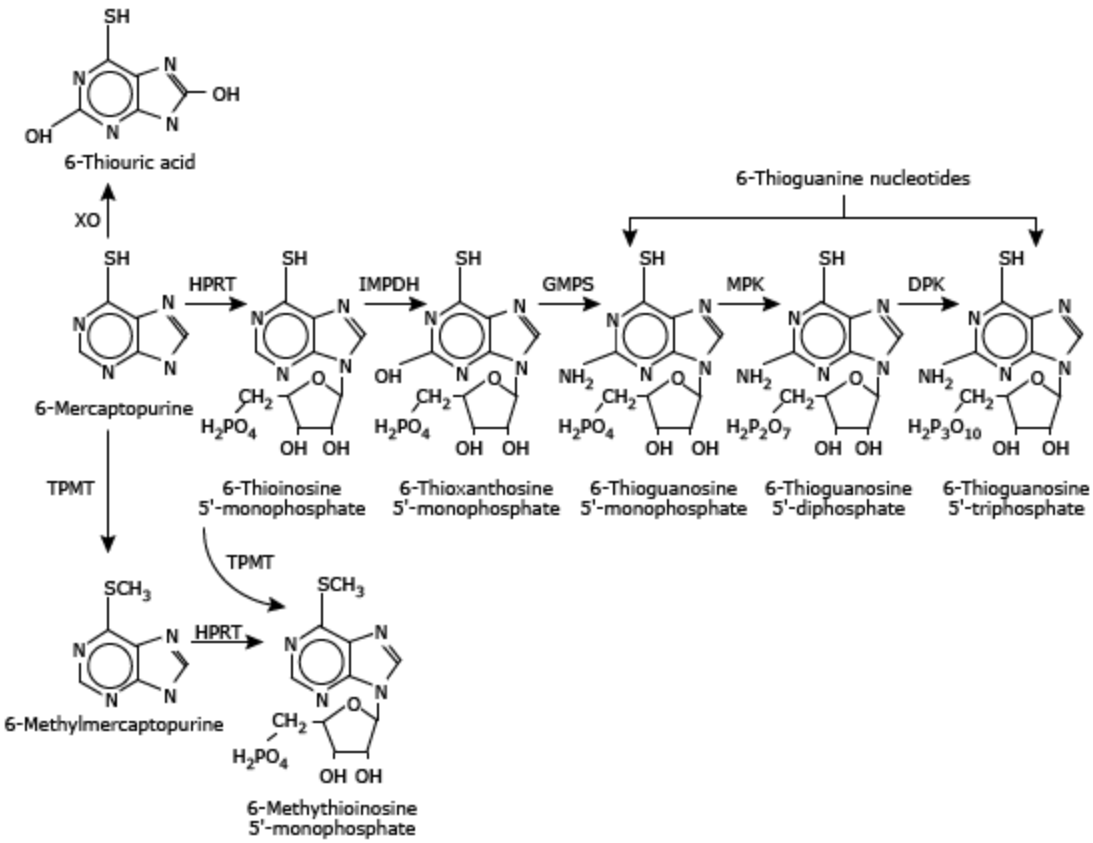
GRAPHICS

6-mercaptopurine metabolism



The initial metabolism of 6-mercaptopurine occurs along the competing routes catalyzed by thiopurine methyltransferase (TPMT), xanthine oxidase (XO), and hypoxanthine phosphoribosyltransferase (HPRT). Further metabolism of the thionucleotide is catalyzed by inosine monophosphate dehydrogenase (IMPDH) and guanosine monophosphate synthetase (GMPS). The diphosphates and triphosphates are formed by their respective monophosphate (MPK) and diphosphate (DPK) kinases.

Graphic 72170 Version 13.0

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