Azathioprine - IBD patients only - Full Clinical Guideline

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Introduction[1]

Inflammatory bowel disease (IBD) is a chronic inflammatory disorder of the gut, divided predominantly into ulcerative colitis (CD) and Crohn's disease (CD). Over the last decade in the UK, there has been a shift in paradigm of the treatment of IBD with a 'top down' or 'rapid step up' approach aimed at altering the natural history early in the course of the disease. Newer biologic drugs are being used, and existing drugs such as thiopurines are being used more effectively, by guiding individual dosing according to pharmacogenetic data and monitoring of drug metabolite levels.

60% of IBD patients receive thiopurines (azathioprine (AZA) and mercaptopurine (MP)) with proven efficacy in maintaining steroid free remission[2]. The evidence for thiopurines in UC is not as strong as in CD, but 53% of patients achieve steroid free remission on AZA compared with 21% on aminosalicylates[3]. So thiopurines are recommended once a patient with UC requires 2 courses of steroids within a year[4]. Thiopurines are commenced earlier in CD where aminosalicylates play little or no role, and have been shown to reduce the need for surgery by 40%[5]. The SONIC trial study showed the benefit of thiopurines in addition to anti-TNF agents in the treatment of CD, probably by reducing antibody formation[6].

Up to a third of patients have to stop thiopurines due to side effects, namely leucopenia (1.3-12.6%), hepatotoxicity (4%) pancreatitis (3%) and gastric intolerance (1.3-6%)[7,8]. Thiopurine-S-methyltransferase (TPMT) activity influences the incidence of adverse effects, particularly bone marrow toxicity. However there is no association with hepatotoxicity or pancreatitis[9].

Thiopurine Metabolism & TPMT

The prodrug AZA is converted non-enzymatically to MP. MP undergoes metabolism to form the active metabolite, thioguanine nucleotides (TGNs). Methylation of MP by TPMT is a critical step in thiopurine metabolism. In Caucasians, complete TPMT deficiency occurs in 1 in 300 individuals[10]. These patients are highly likely to develop severe and potentially fatal myelosuppression if they receive standard doses of AZA or MP. Carriers of a deficient associated allele have around 50% activity and occur in around 1 in 10 of the population[10]. These patients also have a risk of toxicity at standard doses, but this is prevented by initiation of treatment at 50% of the conventional dose. Hence, recommended practice is to check TPMT levels prior to starting therapy and to adjust the dose accordingly. Ultra-high TPMT is associated with a skewed drug metabolism where MP is preferentially metabolised to methylmercaptopurine (MeMP) resulting in lower TGNs associated with a worse clinical response and side effects. This is known as hypermethylation[11].

Thioguanine Nucleotides

TPMT polymorphism only accounts for around 10% of all thiopurine toxicity[12]. Measuring TGNs and MeMP offers a means for therapeutic drug monitoring. This is clinically useful after steady state is reached at 4-6 weeks[13]. Levels between 235 and 450 pmol/^{8}x10^{8} RBCs correlates best with a good clinical response[14,15]. A treatment strategy using TGNs to determine optimal dosing results in improved outcomes in 90% of patients compared with 33% in those not guided by TGNs[13].

Hypermethylation

15-20% of patients with IBD demonstrate hypermethylation when treated with thiopurines[12] (although only 3% of these have an ultra-high TPMT[16]). The usual definition of hypermethylation is a ration of MeMP to TGN of >11. MeMP >5700 results in a higher risk of hepatotoxicity[15].

Allopurinol prevents the breakdown of thiopurines. The combination of low dose thiopurine and 100mg of allopurinol (LDTA) corrects hypermethylation in patients who have failed therapy due to hepatotoxicity or who have sub-therapeutic TGNs[11,17]. When using combination therapy, the dose of AZA or 6MP is reduced to 25-50% of the standard monotherapy dose[18].

Managing Side Effects

Abnormal FBC/Bone Marrow Toxicity

Myelosuppression is associated with low TPMT and with MeMP >11450pmol/^{8}x10^{8} RBCs[19]. In this scenario, use the same regime as for hypermethylation and hepatotoxicity and switch to LDTA. Where leucopenia occurs without hypermethylation, alter the dosing according to blood parameters. In the case of lymphopenia, adjustment is debateable as studies suggest such patients are not at increased risk of infections.

Use of Thiopurine Metabolites

Check TGNs in all patients with symptoms or active disease. Where TGNs are sub-therapeutic, increase dose by 25-50mg. If patient is hypermethylating and TGN sub-therapeutic, either switch to LDTA or split the dose. Dose splitting results in a significant decrease in MeMP levels without reducing TGNs[20].

Gastrointestinal Side Effects

Nausea is common with thiopurines. Changing the time of the dose to later in the day can sometimes alleviate this. Switching to MP can circumvent some cases of AZA induced nausea[21]. A further option is to increase the dose of thiopurine gradually over 2-4 weeks. Switching to LDTA successfully avoids nausea in over half of patients[22].

Hepatotoxicity

4% of patients experience thiopurine related hepatotoxicity. The drug should be stopped until LFTs have normalised followed by commencing LDTA. This remains the case whether the patient is hypermethylating or not.

Pancreatitis

In the 3% of patients who develop pancreatitis, thiopurines must be stopped immediately and not restarted.

Pregnancy

There are good safety data on the use of thiopurines in pregnancy and around the time of conception for women and men and their use is supported by European guidelines[23,24]. There are however, no safety data on the use of allopurinol in pregnancy. Thiopurines should be continued throughout pregnancy after discussion with the patient. Allopurinol should not be started or continued in pregnancy and other treatments should be explored.

Drug Withdrawal

Most centres consider withdrawal after 5 years of treatment if the patient is in clinical remission. Treatment for over 4 years has been shown to increase the risk of non-melanoma skin cancer and lymphoma particularly in those patients over 50 years[25]. There is also an association between long-term thiopurine use and nodular regenerative hyperplasia.

When thiopurines are withdrawn, 1 year clinical relapse rates are 23% in CD and 12% in UC[26].

Conclusion

Thiopurines continue to be the mainstay of treatment for CD and moderate to severe UC. Thiopurine metabolite monitoring in addition to TPMT measurement successfully guides optimised therapy, reducing treatment failure from adverse effects or lack of efficacy.

Practical Guide to Thiopurine Treatment

Pre-treatment investigations and management

FBC, U&E, LFT
TPMT level
Hepatitis B serology (surface antigen and core antibody)
- Treat with reverse transcriptase inhibitors if positive

Hepatitis C serology
- Treatment under specialist guidance if positive

HIV
- Treatment under specialist guidance if positive

EBV IgG
- Treat acute infection with ganciclovir or foscarnet
- Consider alternative treatments if negative

VZV IgG
- If no history of infection, vaccinate patient before initiation of thiopurines as long as steroid free for 3 months

Pneumococcal vaccine (do not delay drug initiation)
Influenza vaccine annually (do not delay drug initiation)

Starting dose

Dependent on TPMT level

Zero	Avoid, consider other treatment	
Low	AZA MP	1-1.25mg/kg 0.5-0.75mg/kg
Normal/High	AZA MP	2-2.5mg/kg 1-1.5mg/kg

Start at target dose – no need for incremental increase

Monitoring blood tests

FBC & LFTs 2 weeks
4 weeks
8 weeks
12 weeks
Then every 3 months

Abnormal FBC/bone marrow toxicity

Full blood count indices	Action for thiopurine drug therapy
WBC 2.5-3.5 x 10^9/l (mild)	Check metabolites, monitor or consider reducing dose
WBC 1.5-2.5 x 10^9/l (moderate)	Stop drug for 1 week, then restart at lower dose with weekly FBC monitoring
WBC <1.5 x 10^9/l (severe)	Withdraw treatment
Lymphopenia 0.5-1.5 x 10^9/l (mild-moderate)	Observe, correct metabolites
Lymphopenia <0.5 x 10^9/l (severe)	Reduce dose
Neutropenia 1-1.5 x 10^9/l (mild)	Observe, correct metabolites
Neutropenia <0.5 x 10^9/l (moderate)	Withdraw treatment. If febrile, consider admitting for G-CSF
Macrocytosis	Continue at current dose, no need to reduce or stop
Thrombocytopenia <150 x 10^9/l	Observe, if ongoing, screen for NRH
Anaemia	Check metabolites; exclude nutritional deficiencies or anaemia of chronic disease. If acute, exclude red cell aplasia

For mild-moderate abnormalities, discuss with patient's consultant before stopping or adjusting dose. Discuss with on call consultant if patient's consultant not available.

In all cases, when stopping or adjusting dose, inform patient's consultant via letter or email.

When to check thiopurine metabolites
All patients with symptoms of active disease.

TGN low	MeMP Normal	Increase dose
TGN low	MeMP high	LDTA/split dose
TGN normal	MeMP normal or high	Consider alternative treatment

GI side effects
Slower dosing increments
Switch to MP
Switch to LDTA

Pancreatitis
Stop thiopurine

Liver Toxicity
Switch to LDTA

REFERENCES

1Warner B et al. Frontline Gastroenterology 2016:1-6.

2 Chevaux JB, Peyrin-Biroulet L, Sparrow MP. Optimizing thiopurine therapy in inflammatory bowel disease. Inflamm Bowel Dis 2011;17:1428–35.

3 Ardizzone S, Maconi G, Russo A, et al. Randomised controlled trial of azathioprine and 5-aminosalicylic acid for treatment of steroid dependent ulcerative colitis. Gut 2006;55:47–53.

4Mowat C, Cole A, Windsor A, et al. Guidelines for the management of inflammatory bowel disease in adults. Gut 2011;60:571–607.

5 Chatu S, Subramanian V, Saxena S, et al. The role of thiopurines in reducing the need for surgical resection in Crohn's disease: a systematic review and meta-analysis. Am J Gastroenterol 2014;109:23–34; quiz 35.

6 Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med 2010;362:1383–95.

7 Siegel CA, Sands BE. Review article: practical management of inflammatory bowel disease patients taking immunomodulators. Aliment Pharmacol Ther 2005;22:1–16.

8 Schwab M, Schäffeler E, Marx C, et al. Azathioprine therapy and adverse drug reactions in patients with inflammatory bowel disease: impact of thiopurine S-methyltransferase polymorphism. Pharmacogenetics 2002;12:429–36.

9 Dong XW, Zheng Q, Zhu MM, et al. Thiopurine S-methyltransferase polymorphisms and thiopurine toxicity in treatment of inflammatory bowel disease. World J Gastroenterol 2010;16:3187–95.

10 Weinshilboum RM, Sladek SL. Mercaptopurine pharmacogenetics: monogenic inheritance of erythrocyte thiopurine methyltransferase activity. Am J Human Genetics 1980;32:651–62.

11 Blaker PA, Arenas-Hernandez M, Smith MA, et al. Mechanism of allopurinol induced TPMT inhibition. Biochem Pharmacol 2013;86:539–47.

12 Ansari A, Arenas M, Greenfield SM, et al. Prospective evaluation of the pharmacogenetics of azathioprine in the treatment of inflammatory bowel disease. Aliment Pharmacol Ther 2008;28:973–83.

13 Smith M, Blaker P, Patel C, et al. The impact of introducing thioguanine nucleotide monitoring into an inflammatory bowel disease clinic. Int J Clin Pract 2013;67:161–9.

14 Moreau AC, Paul S, Del Tedesco E, et al. Association between 6-thioguanine nucleotides levels and clinical remission in inflammatory disease: a meta-analysis. Inflamm Bowel Dis 2014;20:464–71.

15 Dubinsky MC, Lamothe S, Yang HY, et al. Pharmacogenomics and metabolite measurement for 6-mercaptopurine therapy in inflammatory bowel disease. Gastroenterology 2000;118:705–13.

16 Colombel JF, Ferrari N, Debuysere H, Genotypic analysis of thiopurine S-methyltransferase in patients with Crohn's disease and severe myelosuppression during azathioprine therapy. Gastroenterology 2000;118:1025–30.

17 Ansari A, Patel N, Sanderson J, et al. Low-dose azathioprine or mercaptopurine in combination with allopurinol can bypass many adverse drug reactions in patients with inflammatory bowel disease. Aliment Pharmacol Ther 2010;31:640–7.

18 Sparrow MP, Hande SA, Friedman S, et al. Allopurinol safely and effectively optimizes tioguanine metabolites in inflammatory bowel disease patients not responding to azathioprine and mercaptopurine. Aliment Pharmacol Ther 2005;22:441–6.

19 Hindorf U, Lindqvist M, Hildebrand H, et al. Adverse events leading to modification of therapy in a large cohort of patients with inflammatory bowel disease. Aliment Pharmacol Ther 2006;24:331–42.

20 Shih DQ, Nguyen M, Zheng L, et al. Split-dose administration of thiopurine drugs: a novel and effective strategy for managing preferential 6-MMP metabolism. Aliment Pharmacol Ther 2012;36:449–58.

21 Kennedy NA, Rhatigan E, Arnott ID, et al. A trial of mercaptopurine is a safe strategy in patients with inflammatory bowel disease intolerant to azathioprine: an observational study, systematic review and meta-analysis. Aliment Pharmacol Ther 2013;38:1255–66.

22. Halevy S, Ghislain PD, Mockenhaupt M, et al. EuroSCAR Study Group. Allopurinol is the most common cause of Stevens-Johnson syndrome and toxic epidermal necrolysis in Europe and Israel. J Am Acad Dermatol 2008;58:25–32.

23 Coelho J, Beaugerie L, Colombel JF, et al. Pregnancy outcome in patients with inflammatory bowel disease treated with thiopurines:cohort from the CESAME Study. Gut 2011;60:198–203.

24 Teruel C, López-San Román A, Bermejo F, et al. Outcomes of pregnancies fathered by inflammatory bowel disease patients exposed to thiopurines. Am J Gastroenterology 2010;105:2003–8.

25 Beigel F, Steinborn A, Schnitzler F, et al. Risk of malignancies in patients with inflammatory bowel disease treated with thiopurines or anti-TNF alpha antibodies. Pharmacoepidemiol Drug Saf 2014;23:735–44.

26 Kennedy NA, Kalla R, Warner B, et al. Thiopurine withdrawal during sustained clinical remission in inflammatory bowel disease: relapse and recapture rates,

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