

Clinical Use and Practical Application of TPMT Enzyme and 6-Mercaptopurine Metabolite Monitoring in IBD

Ernest G. Seidman, MD

Division of Gastroenterology, Hepatology, and Nutrition, Faculty of Medicine, University of Montreal, Montreal, Canada

6-mercaptopurine (6-MP) and its parent drug azathioprine (AZA) have been proven to be effective for both steroid-dependent and chronically active, or steroid-resistant inflammatory bowel disease, as well as for the prevention of relapse. Concerns about toxicity, delayed onset of action, and therapeutic failure (1 out of 3 patients) have restricted their use. Recent pharmacogenetic advances have led to the development of novel strategies to optimize and individualize therapy with AZA and 6-MP, maximizing efficacy while minimizing toxicity. We have defined a range of optimal therapeutic 6-MP metabolite levels, as well as an association of metabolite levels with medication-induced toxicity and the genotype of the main catabolic enzyme, thiopurine methyltransferase (TPMT). Measurement of 6-MP metabolite levels and TPMT molecular analysis provide clinicians with useful tools for optimizing therapeutic response to 6-MP/AZA, as well as for identifying individuals at increased risk for drug-induced toxicity.

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It is well established that the immunomodulatory agents 6-mercaptopurine (6-MP) and its pro-drug azathioprine (AZA) have significant beneficial effects on the long-term clinical course of inflammatory bowel disease (IBD). Their efficacy has been demonstrated in both pediatric and adult patients for the treatment of key, specific indications (summarized in Table 1). Placebo-controlled trials have demonstrated that AZA and 6-MP improve long-term remission rates for both ulcerative colitis and Crohn's disease (CD). Significant steroid-sparing effects

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“...Convert a treatment failure into a responder.”



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“Genetically determined variations in the activity of TPMT can lead to differences in the likelihood of response to and toxicity from 6-MP and AZA.”

“Determining polymorphisms of TPMT by genotyping has been shown to be a clinically useful and **cost-effective strategy** to help clinicians identify patients at risk for toxicity from 6-MP and AZA.”

Optimizing therapeutic response and decreasing the risk of toxicity

- TPMT genotyping and measuring 6-MP metabolite levels are useful tools that allow physicians to individualize therapy and achieve optimal therapeutic response while decreasing the risk of toxicity

Genetic determinants of thiopurine metabolism

Gene Frequency	Genotype	Enzyme Activity
89%	Homozygous normal	Normal to high
11%	Heterozygous	Intermediate
0.33%	Homozygous deficient	Low to absent

Adapted from:

Seidman EG. p S33, Table 3.

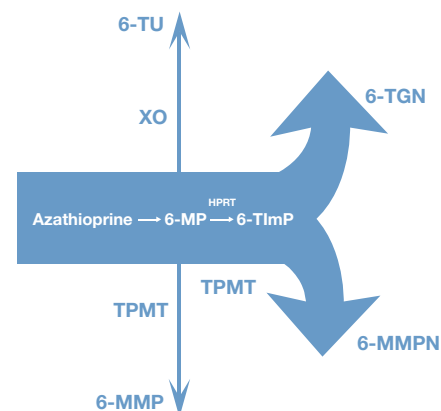
- 89% of patients may tolerate full dosing** of thiopurine from the beginning
- For these patients, it is not necessary to “start low and go slow”

Clinical utility of TPMT genotyping prior to drug thiopurine therapy

- May reduce time to response
- Allows “tailored” starting dose
- Identifies patients in whom thiopurine therapy should be avoided
- Reduces the risk of leukopenia

Metabolic pathways of thiopurine drug metabolism

- Patients metabolize thiopurine differently and the efficacy and toxicity can vary from patient to patient
 - 6-TGN is associated with efficacy and the potential risk of myelotoxicity
 - 6-MMPN is associated with the potential risk of hepatotoxicity



Adapted from:

Seidman EG. p S32, Figure 2.

Monitoring metabolite levels after initiating therapy may...

- Increase response rates
- Identify many of the reasons why patients do not respond
- Identify nonadherence
- Identify the causes of myelotoxicity and hepatotoxicity
- Diminish steroid exposure

Clinical utility of using metabolites to benchmark response

- Provides an individual therapeutic goal for future comparison
- Identifies probable reason for treatment failure (ie, nonadherence)
- Identifies potentially toxic metabolite levels

“Metabolite levels are monitored to the point of clinical response, serving as a baseline measure for future comparison.”

Reasons for thiopurine treatment failure in patients with IBD

Reason	Failure (%)	6-TGN Level (pmol/8 × 10 ⁸ RBC)	6-MMPN Level (pmol/8 × 10 ⁸ RBC)
Inadequate dose	74	Low (<230)	Low (<5700)
Predominant TPMT	15	Low (<230)	High (>5700)
Nonadherence	6	Low (<<230)	Low (<<5700)
Drug failure	5	Normal (230-400)	Normal (<5700)

Adapted from:

Seidman EG. p S34, Figure 5.

“[Establishing baseline metabolite levels] allows the clinician to determine whether a late relapse is due to patient nonadherence to therapy...[rather than] incorrectly [assuming] that the dose prescribed was inadequate.”

*Data on file.

Summary

It is highly recommended that:

1. TPMT genotype or phenotype be determined before initiation of thiopurine therapy in order to individualize and optimize therapy from the very beginning
2. Metabolite levels be measured to reach and maintain therapeutic goal
3. Baseline metabolite levels be established and monitored to help identify the reason for treatment failure

PROMETHEUS PRO-PredictRx TPMT® Genetics

- Classify patients for individualized starting dose

PROMETHEUS PRO-PredictRx® Metabolites

- Optimize ongoing dosing to reach and maintain therapeutic goal

Prometheus diagnostic services provide important information to aid in the diagnosis and management of certain diseases and conditions. How this information is used to guide patient care is the responsibility of the physician.

Ongoing monitoring of CBCs and LFTs is recommended for patients on thiopurine therapy.

