



Optimizing 6-mercaptopurine and azathioprine therapy in the management of inflammatory bowel disease

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dosing of 6-MP.

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Abstract

The thiopurine drugs, 6-mercaptopurine (6-MP) and azathioprine, are efficacious in the arsenal of inflammatory bowel disease (IBD) therapy. Previous reports indicate that 6-thioguanine nucleotide (6-TGN) levels correlate with therapeutic efficacy, whereas high 6-methylmercaptopurine (6-MMP) levels are associated with hepatotoxicity and myelotoxicity. Due to their complex metabolism, there is wide individual variation in patient response therein, both in achieving therapeutic drug levels as well as in developing adverse reactions. Several strategies to optimize 6-TGN while minimizing 6-MMP levels have been adopted to administer the thiopurine class of drugs to patients who otherwise would not tolerate these drugs due to side-effects. In this report, we will review different approaches to administer the thiopurine medications, including the administration of 6-mercaptopurine in those unsuccessfully treated with azathioprine; co-administration of thiopurine with allopurinol; co-administration of thiopurine with anti-tumor necrosis factor α ; 6-TGN administration; desensitization trials; and split

INTRODUCTION

Inflammatory bowel disease (IBD) encompassing Crohn's disease (CD) and ulcerative colitis (UC), is a chronic inflammatory disorder caused by dysregulated immune responses in a genetically predisposed individual. Given the role that the immune system plays in IBD, the hallmark of therapy is immune modulation. The thiopurine drugs, 6-mercaptopurine (6-MP) and its prodrug azathioprine (AZA), remain the mainstay of immunomodulator therapy for IBD and are indicated in steroid-dependent and -refractory patients, as prophylaxis in CD^[1-3]. Chebli found that AZA maintained steroid-free clinical remission for three years in UC patients, previously steroid-dependent^[2]. Of note, however, AZA has not been shown to be effective in treating active UC flare^[4]. Rather, thiopurines have also been noted to induce and maintain remission in UC and CD patients, more effectively than 5-aminosalicylic acid^[1,5-10]. However efficacious, their use

is often limited, as an estimated 30% to 50% of patients discontinue these drugs due to either side-effects or lack of clinical efficacy^[11-13]. The lack of response to these immunomodulators has been attributed to differences in individual variations in drug metabolism^[14,15]. The 6-thioguanine nucleotide (6-TGN) metabolite of 6-MP and AZA appears to be the predominant active metabolite responsible for therapeutic efficacy, whereas 6-methylmercaptapurine (6-MMP) levels correlate with the risk of hepatotoxicity and possibly myelotoxicity^[15,16]. Theoretically, if the thiopurine metabolite profile can be shifted to 6-TGN, a greater percentage of IBD patients would benefit from immunomodulator therapy. A meta-analysis has confirmed that higher 6-TGN levels are associated with remission among IBD patients^[17]. In this review, we will discuss the thiopurine metabolic pathway, monitor the drug metabolite levels, and evaluate the different approaches that have been developed to enhance clinical efficacy and minimize the side-effects of AZA and 6-MP.

THIOPURINE METABOLIC PATHWAY

To achieve the active cytotoxic form, AZA is metabolized *via* a series of biochemical pathways summarized in Figure 1. Initially, approximately 90% is non-enzymatically cleaved to 6-MP in the liver^[18,19]. There are three competitive metabolic pathways in 6-MP metabolism. It can be inactivated to 6-thiouric acid (6-TU) *via* xanthine oxidase (XO), activated to 6-MMP *via* thiopurine methyltransferase (TPMT), or to the therapeutic 6-TGN *via* enzymes hypoxanthine phosphoribosyl transferase (HPRT), inosine monophosphate dehydrogenase (IMPDH), and guanosine monophosphate synthetase (GMPS)^[11,20,21]. A complete understanding of its mode of action is unknown^[19]; however, based on its structural similarity to the purine guanine, 6-TGN is a purine antagonist that inserts within the DNA of leukocytes^[22]. Intracellular build up of 6-TGN is thought to be the cytotoxic form that inhibits DNA synthesis and downstream T cell proliferation for its immunosuppressive activity^[20,23,24]. Using a genome-wide expression profiling approach, 6-TGN was found to inhibit several immune and inflammation-related genes including tumor necrosis factor-related apoptosis-inducing ligand, tumor necrosis factor receptor superfamily member 7, and α 4-integrin in activated but not resting T lymphocytes^[25]. Thus, 6-TGN may additionally exert its immunosuppressive effect by down-regulating the expression of pro-inflammatory and gut-homing factors. Another report found that the immunosuppressive role of thiopurine medications may in part be due to its metabolite 6-thioguanine triphosphate (6-TGTP) suppression of the Rac1 protein, which participates in T cell maturation and proliferation, thus inducing T lymphocyte apoptosis^[19,26].

MONITORING THIOPURINE METABOLITE LEVELS

Because AZA is 55% of 6-MP by molecular weight and

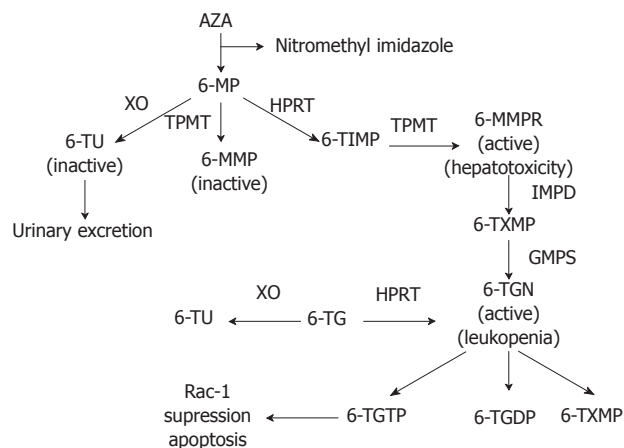


Figure 1 Thiopurine metabolic pathway. Metabolic pathway for AZA and 6MP is shown in the diagram. AZA: Azathioprine; 6-MP: 6-mercaptopurine; 6-TU: Thiouric acid; 6-MMP: 6-methylmercaptapurine; TIMT: Thiopurine methyltransferase; 6-MMPR: Methyl-mercaptapurine ribonucleotide; TXMP: 6-thioxanthosine monophosphate; 6-TGN: Thioguanine nucleotide; 6-TG: Thioguanine; 6-TGDP: 6-thioguanine diphosphate; 6-TGTP: 6-thioguanine triphosphate; XO: Xanthine oxidase; TPMT: Thiopurine methyltransferase; HPRT: Hypoxanthine phosphoribosyl transferase.

88% of AZA is converted to 6-MP, historically, thiopurines are dosed by the patient's weight; the maintenance dose of AZA is 2-2.5 mg/kg per day and 6-MP is dosed at half that of AZA, or 1-1.5 mg/kg per day in IBD patients^[1,22,7-29]. Individual variation in drug metabolism account for the differences in therapeutic efficacy and development of adverse reactions^[30,31]. Fortunately, advances in thiopurine metabolite monitoring can help predict which patients are more at risk of developing side effects, allowing for adjustments in drug dosages^[11,15].

TPMT is a key enzyme whose activity determines the level of 6-MMP as well as 6-TGN metabolite levels^[15,20,24,30]. TPMT methylates 6-MP to 6-MMP and 6-TIMP to 6-methylmercaptapurine ribonucleotide (MMPR) (Figure 1)^[15]. Elevated levels of 6-MMP (> 5700 pmol/ 8×10^8 erythrocytes) are associated with hepatotoxicity, whereas 6-TGN is the metabolite responsible for the therapeutic activity of thiopurines. Monitoring the thiopurine metabolite levels can help to optimize immunomodulator therapy and minimize adverse events. A retrospective study showed that patients who did not respond to AZA or 6-MP either had a high 6-MMP concentration or 6-MMP/6-TGN ratio^[12]. Furthermore, a subset of IBD patients preferentially metabolize thiopurines to the hepatotoxic 6-MMPR which explains why some patients develop toxic metabolite accumulation, side effects and ultimately cannot be maintained on thiopurine therapy^[30]. Even though 6-TGN is associated with therapeutic immunosuppressive activity, an excess amount of this metabolite poses an increased risk for myelosuppression^[32]. The therapeutic efficacy of 6-MP or AZA are correlated with 6-TGN levels between 235-450 pmol/ 8×10^8 erythrocytes^[15,22,33,34]. Because several studies have shown that weight-based dosing is poorly correlated with 6-TGN levels^[16,35,36], monitoring thiopurine metabolite levels can help optimize immunomodulatory therapy while mini-

mizing adverse effects^[15,30,34].

Differences in patient response to thiopurines may in part be due to patient-specific metabolism and genetic variation^[30]. TPMT activity is inversely related to clinical response to AZA^[11]. Different genetic polymorphisms code for the level of TPMT activity^[37]. 0.3% of the Caucasian population are homozygous for low enzyme activity; 11% are heterozygous and 89% are homozygous for high enzyme activity^[38]. Allelic frequency patterns vary among different ethnic groups. In Caucasian populations, intermediate or low TPMT activity is most frequently associated with TPMT*2, TPMT*3A or TPMT*3C alleles^[38], while in African-Americans, TPMT*3C is the most prevalent variant allele^[39]. Wild-type or heterozygous TPMT deficient patients have high TPMT activity > 14 units/mL RBC, which were associated with higher levels of 6-MMP and lower levels of 6-TGN, and thus a decreased likelihood of achieving complete remission (termed 6-MP resistance) and increased risk for hepatotoxicity^[11,13,30]. Dose escalation of thiopurine level may optimize 6-TGN levels, but must be done under caution given that TPMT also catalyzes the formation of the toxic metabolite 6-MMP^[40]. A meta-analysis found that TPMT polymorphisms are related to adverse drug reactions and myelotoxicity, but not hepatotoxicity or pancreatitis^[37]. It is thought that the higher level of TPMT activity may cause higher 6-MP catabolism resulting in higher 6-MMP and decreased 6-TGN levels^[11]. Low TPMT and thus high 6-TGN is associated with a higher risk for leukopenia^[13,15].

Studies have found that checking TPMT activity may be cost-effective as compared to standard therapeutic dose administration^[33,41]. Traditionally, AZA or 6-MP was started at a low dose and progressively titrated up because of safety concerns (bone marrow suppression, hepatotoxicity, etc.). Using this strategy, time to initial response is delayed and can take up to 6 mo to reach therapeutic response^[6,33,42,43]. Compared to traditional thiopurine dosing, monitoring TPMT can allow faster achievement of initial response (22.4 wk *vs* 18.9 wk) and lower costs at 1 year (\$7142 *vs* \$3861)^[33]. Thus, patients found to have normal TPMT could have dose escalation sooner therefore avoiding delay in achieving response^[33]. The cost-effectiveness of measuring TPMT activity was independently shown in a separate study^[41]. Furthermore, awareness of TPMT activity can help to avoid potential deleterious consequences of thiopurine therapy. For example, in patients with low TPMT activity, a lower initiation dose or avoidance of either 6-MP or AZA is recommended due to risks of leukopenia^[16,44]. Albeit, TPMT activity monitoring is not universally available to all practitioners; in these cases, thiopurine may be started at a low-dose (50 mg daily) and titrated up with weekly monitoring of CBC and liver function tests during the first 2 mo, and once every 3 mo thereafter^[20].

APPROACHES TO OPTIMIZING THIOPURINE METABOLITES

Use of 6-MP in patients who are intolerant of AZA

In addition to bone marrow suppression and hepatotoxicity,

early hypersensitivity reactions including fever and gastrointestinal side effects including diarrhea, nausea, and emesis can occur in as many as 10% of patients^[45]. These adverse reactions often cause IBD patients to discontinue thiopurine therapy. Several studies have shown that among patients intolerant of AZA, 6-MP may be a safe and effective alternative^[29,45,46]. One study showed that 20 of 29 (69%) IBD patients with a history of AZA hypersensitivity tolerated 6-MP^[46]. An AZA to 6-MP change appears to be more effective in UC compared to CD patients as by the end of the first year, none of the CD patients were maintained on 6-MP^[46]. In addition to hypersensitivity reactions, up to 60% of IBD patients with AZA intolerance due to nausea, emesis, and flu-like illness tolerated switching to 6-MP^[45]. In contrast, patients who discontinued AZA due to hepatotoxicity or pancreatitis were less likely to tolerate 6-MP^[45]. Another study found that 48% of patients previously intolerant to AZA due to myalgia and arthralgia were able to tolerate 6-MP^[46]. Another report showed that 11 of 15 (11 CD, 4 UC) patients (73.3%) who discontinued AZA due to epigastric pain, nausea and vomiting tolerated 6-MP and reached therapeutic goals^[47]. A retrospective study showed that 19 out of 140 patients discontinued AZA therapy (4 patients for clinical inefficacy, 13 due to side-effects, 2 due to leucopenia)^[48]. Of these 19 patients, 11 (58%) tolerated the switch to 6-MP^[48]. Consistent with the above findings, another report showed that 6 of 11 patients who initially could not tolerate AZA, were able to tolerate 6-MP and achieve response^[18]. The reasons behind the observation that 6-MP bypasses the adverse reactions caused by AZA are unclear, but may in part be due to the nitro-imidazole structure that is released as AZA is cleaved to 6-MP^[49].

Based upon the above studies, we propose that 6-MP should be considered in IBD patients who require continuing immunosuppressive therapy but are intolerant of AZA. We caution that there has been variable success among those who are switched to 6-MP (Table 1), and unfortunately many of the same reactions to AZA develop with 6-MP over time.

Use of AZA in 6-MP intolerant patients

The converse treatment strategy of administering AZA to patients who did not tolerate initial 6-MP therapy has not proved as effective^[48,50,51]. In a trial of AZA after 6-MP adverse reactions, similar side-effect profiles were seen^[18,48,50,51]. This is likely due to the fact that AZA is converted in the liver to 6-MP (Figure 1), thereby, yielding similar adverse reactions (Table 1). Based upon the lack of clinical efficacy, we do not recommend using AZA in patients who were previously intolerant of 6-MP.

Desensitization

Some investigators propose desensitization in the subset of patients who experience hypersensitivity reactions to AZA or 6-MP within the first month of treatment. Korrelitz *et al*^[51,52] retrospectively reviewed 591 charts of IBD

Table 1 Summary of strategies to optimize thiopurine metabolite levels

| Method | Effectiveness (%) | Side effect |
|-----------------------------------|-------------------------------------|---|
| AZA to 6-MP | 48-73 ^[45-48] | Nausea, vomiting, hepatotoxicity, neutropenia, pancreatitis |
| 6-MP to AZA | Not effective ^[48,50,51] | Nausea, vomiting, hepatotoxicity, neutropenia, pancreatitis |
| Desensitization | 25 ^[51] | Hypersensitivity reaction |
| Combination infliximab/thiopurine | 25 ^[72,74] | Lymphoma, infection |
| 6-TG | 46-82 ^[50,58] | NRH, veno-occlusive disease and possible tumor |
| Allopurinol supplementation | 25-75 ^[68,69] | Skin rash, renal impairment, leukopenia |
| Split-dosing | 60 ^[75] | Reduces 6-MP, AZA associated adverse effects |

AZA: Azathioprine; 6-MP: 6-mercaptopurine; NRH: Nodular regenerative hyperplasia; 6-TG: 6-thioguanine.

patients treated with 6-MP. Four of 16 patients who had early hypersensitivity reactions were successfully desensitized to 6-MP or AZA and achieved long-term clinical remission. One patient tolerated the direct switch from 6-MP to AZA. Of the remaining 11 patients, 5 needed surgery, 2 were changed to methotrexate (MTX), and 4 had chronic symptoms. In this study, desensitization began at one-quarter tablet per day, with an increase in the dose every 3 d for several weeks until a full dose was reached^[51,52]. A similar case report describes a CD patient who developed skin rash after 4 wk of treatment with AZA^[53]. Upon drug withdrawal, the rash resolved. A skin test was positive for AZA allergy, suggesting an IgE mediated hypersensitivity; and the patient was desensitized with AZA, with the patient's CD successfully in remission^[53]. Another case report describes a CD patient who developed a macular, erythematous truncal rash and fever after treatment with 6-MP^[54]. This patient was able to tolerate 6-MP after desensitization^[54]. The process of desensitization for patients with hypersensitivity reactions to AZA or 6-MP may be an empiric strategy for maintenance of immunomodulator therapy. However, we caution that more studies are needed to confirm the efficacy of this strategy.

6-thioguanine

As a possible alternative to those who cannot be maintained on 6-MP or AZA, treatment using 6-TG has been proposed. This drug has been used in children with acute lymphoblastic leukemia^[55]. Compared to AZA, 6-TG is directly converted to 6-TGN by HPRT (Figure 1)^[56,57]. Since 6-TG is a poor substrate for TPMT, hepatotoxic 6-MMP production would be low^[50,55]. Therefore, 6-TG bypasses several of the steps in thiopurine metabolism that are responsible for producing toxic metabolite

build-up and its association with the aforementioned potential adverse effects^[13,50]. One study found that of the 49 CD patients who were either resistant or intolerant to AZA or 6-MP, 46% of patients at 6 mo and 79% of patients at 12 mo were in remission and none of the patients developed pancreatitis or bone marrow toxicity^[58]. Although up to 82% of patients tolerated 6-TG^[50], this drug has been associated with several possible toxicities, notably nodular regenerative hyperplasia (NRH). One study found that the prevalence of NRH to be 16 out of 26 (62%) biopsies taken from patients treated with 6-TG^[59]. Several studies further found that the incidence of NRH associated with 6-TG use varied from 4%-27% among thiopurine naive patients (Table 1)^[60-62]. Other 6-TG associated adverse effects include secondary liver tumors, veno-occlusive disease, and other vascular liver pathologies^[50,58,63-65]. Formal dose-ranging studies for 6-TG are lacking and only limited data are available on the therapeutic efficacy and dosing regimes^[13]. As a general rule, dosage should not exceed 25 mg daily, as higher dosing has been associated with an increased risk of developing NRH^[13,66].

6-TG can be considered a rescue drug in IBD patients intolerant of or refractory to AZA or 6-MP. However, given the potential complications including NRH, and the small number of long-term safety monitoring and limited formal dose-range studies, we do not recommend 6-TG therapy at this time.

Allopurinol supplementation

In some patients, with AZA or 6-MP dose escalation, rather than achieving therapeutic levels of TGN, 6-MMP levels increase and resultant hepatotoxicity ensues^[67]. These patients are known as preferential 6-MMP metabolizers^[50]. Among IBD patients with high TPMT activity who favor 6-MMP production with reduced 6-TGN levels, adding the XO inhibitor allopurinol can favor the production of 6-TGN over 6-MMP^[68,69]. The addition of allopurinol to 6-MP or AZA resulted in improved disease activity as measured by the partial Harvey Bradshaw index in CD and Mayo scores in UC patients; decreased prednisone maintenance dose, and improved liver function laboratory values^[68,69]. However, at the 18 mo follow-up, 25% of these patients were escalated to anti-tumor necrosis factor (TNF) α therapy and 2 required surgery.

The exact mechanism of shifting thiopurine metabolites from 6-MMP to 6-TGN by the XO inhibitor is unknown, but may involve reduced production of the inactive thiouric acid (TU) metabolite in favor of the cytoactive metabolites 6-MMP and 6-TGN^[67,70,71]. However, if XO inhibition favors MMP and TGN production, then the toxic 6-MMP would also be expected to increase (Figure 1). Interestingly, allopurinol does not increase the level of 6-MMP or its associated hepatotoxicity, but mainly shifts the metabolite to 6-TGN.

Potential side effects of allopurinol include skin rash and renal impairment^[68]. In addition, the addition of allopurinol to thiopurine therapy may lead to supra-

therapeutic levels of 6-TGN, leading to leukopenia^[40,68]. Therefore, it is recommended that if allopurinol is used in combination with 6-MP or AZA, the dose of thiopurine medications should be reduced by at least 50% with close laboratory monitoring for leukopenia with weekly CBC monitoring during the first month, followed by every other week for the next month.

Combination therapy: Thiopurine and anti-TNF

Anti-TNF therapies are generally used for patients who are refractory to first-line medications^[72,73]. Colombel *et al.*^[72] conducted a randomized, double blind study of moderate-to-severe CD patients, comparing infliximab and AZA alone *vs* in combination and found that the primary endpoint, steroid-free remission at 26 wk, was achieved in a greater number among those treated in combination *vs* monotherapy. Mucosal healing, a secondary endpoint was also greater among patients who received combination therapy. These patients were immunosuppressant- and biologic therapy-naïve patients. Caution must be used, however, as studies have found an increased risk of non-Hodgkin's lymphoma in patients treated with anti-TNF with a history of thiopurine use^[74].

Split dose administration of thiopurines

As discussed above, patients who are preferential 6-MMP metabolizers exhibit high 6-MMP levels with subtherapeutic 6-TGN levels when thiopurines are dosed in the traditional weight-based, once-a-day fashion. 6-MP/AZA dose escalation in this subset of patients in an attempt to push the 6-TGN level into the "therapeutic range"-often results in dose-dependent leukopenia, transaminitis and/or flu-like symptoms (headache, nausea, myalgia, fatigue, general malaise). Overproduction of 6-MMP and side-effects resolve with dose reduction, but the lower dose often fails to adequately suppress IBD disease activity, resulting in suboptimal symptom control.

Anecdotally, we observed that simply splitting the daily dose of thiopurine (e.g., 50 mg *BID* rather than 100 mg once daily) can reduce the 6-MMP metabolites while maintaining 6-TGN levels. To confirm our observation, we performed a retrospective chart review of patients with baseline 6-MMP levels greater than $7000 \text{ pmol}/8 \times 10^8$ red blood cells (RBC) who underwent split dosing ($n = 20$). Dividing the daily thiopurine dose led to a significant reduction in 6-MMP levels ($11\,879 \text{ vs } 5955 \text{ pmol}/8 \times 10^8$ RBC; $P < 0.0001$) without adversely affecting clinical disease activity (HBI) or 6-TGN levels ($250 \text{ vs } 227 \text{ pmol}/8 \times 10^8$, $P = \text{NS}$)^[75]. Side-effects associated with 6-MMP, such as abnormal liver function test (LFT), leukopenia and flu-like symptoms, improved in seven of eight patients^[75]. After a mean follow-up of 42 mo, 12 of 20 patients were able to be maintained on a split dose of 6-MP with control of their IBD activity^[75]. To our knowledge, this is the first study to demonstrate the effectiveness of dose splitting on preferential metabolism. This approach has several advantages over other strategies. Dose splitting does not sacrifice potential efficacy associated with

dose reduction, and may even allow for further upward titration of thiopurine to efficacy if needed. It avoids the introduction of possible additional medication side effects as can be seen with co-administration of allopurinol and the potential cost burden of designer biologic inventions. This maneuver is relatively simple for both patients and practitioners alike.

Independent studies are needed to confirm that split-dose administration of thiopurine is an effective approach to manage 6-MMP preferential metabolizers. However, in an IBD patient who might otherwise not tolerate immunomodulator therapy and require ongoing steroid exposure and/or escalation of therapy to biologics, splitting the daily dose of 6MP or AZA may be attempted.

POTENTIAL RISK OF LYMPHOPROLIFERATIVE DISEASE

Thiopurines have been linked with chromosomal abnormalities and an increased risk of lymphoma among rheumatoid arthritis patients^[76]. Whether the same risk exists in IBD patients is controversial. A meta-analysis of six studies showed a four-fold increased risk of developing lymphoma among IBD patients treated with immunomodulators^[77]. Similarly, in the CESAME prospective cohort study by Beaugerie, a five-fold increased risk of lymphoproliferative diseases was shown among IBD patients on thiopurines^[78]. Whether this risk stems from underlying disease or iatrogenic medication is unclear. Studies have shown that the risk is greater in IBD patients who are male and between 15 to 40 years old^[79,80]. One study focused on hepatosplenic T-Cell lymphoma and noted cases among men younger than 35 years who had been treated with either anti-TNF and thiopurines or thiopurine monotherapy^[79]. In contrast, a study by Vos *et al.*^[81] found no increased risk of lymphoma among a nationwide study of 17 834 IBD patients. Interestingly, however, they did find an association between Epstein-Barr Virus-positive lymphoma and thiopurine use. EBV-positive lymphoma implies the effect of immunosuppression as a factor^[77,80,81]. Nevertheless, the consensus has been that the benefits of thiopurines outweigh the risk^[77,82]. Lewis *et al.*^[82] conducted a decision analysis and found that a 9.8-fold increase in lymphoma is needed to favor an alternative therapy over AZA. Further studies are needed, as it has yet to be determined how this risk changes with discontinuation of thiopurines^[77].

CONCLUSION

Given the complex metabolism of thiopurines and the individual variability among patients in response to this medication, various dosing strategies have been adopted. Several approaches have been promising among patients who develop toxicities to the initial strategy. However, no single strategy has proven completely effective in all patients. Further studies will inevitably provide more in-

formation to assist in optimizing administration of these vital IBD medications. This is significant given that there are a limited number of medications available in the IBD arsenal. In all dosing strategies, however, close monitoring of metabolites as well as determination of pharmacogenetics are pivotal for patient safety and medication efficacy.

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