

How I treat my inflammatory bowel disease-patients with thiopurines?

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Author contributions: de Boer NKH was the guarantor of the article; Meijer B completed the first draft of the manuscript; Mulder CJJ, van Bodegraven AA and de Boer NKH critically revised the manuscript; Meijer B finalized the article.

Conflict-of-interest statement: There is no conflict of interest associated with any of the senior author or other coauthors contributed their efforts in this manuscript.

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Manuscript source: Invited manuscript

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Received: July 21, 2016
Peer-review started: July 21, 2016
First decision: September 5, 2016
Revised: September 12, 2016
Accepted: October 5, 2016
Article in press: October 7, 2016
Published online: November 6, 2016

Abstract

Thiopurines are essential drugs to maintain remission in patients with inflammatory bowel disease (IBD). Thiopurines used in IBD are azathioprine (2.0-2.5 mg/kg), mercaptopurine (1.0-1.5 mg/kg) and thioguanine (0.2-0.3 mg/kg). However, mainly due to numerous adverse events associated with thiopurine use, almost 50% of the patients have to discontinue conventional thiopurine treatment. Extensive monitoring and the application of several treatment strategies, such as split-dose administration, co-administration with allopurinol or dose reduction/increase, may increase the chance of successful therapy. With this review, we provide practical information on how thiopurines are initiated and maintained in two thiopurine research centers in The Netherlands. We provide clinical information concerning safety issues, indications and management of therapy that may serve as a guide for the administration of thiopurines in IBD patients in daily practice.

Key words: Thiopurines; Azathioprine; Mercaptopurine; Thioguanine; Inflammatory bowel disease; Therapeutic drug monitoring; Pregnancy; Metabolites

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Core tip: Conventional thiopurine therapy with azathioprine and mercaptopurine in inflammatory bowel disease is associated with several adverse events causing cessation of therapy in up to half of the patients. On the contrary, thiopurine therapy is often unnecessarily discontinued. In this practical review, we provide information on how thiopurine therapy is initiated and maintained using periodical laboratory tests and the application of various treatment strategies (including the administration of a third thiopurine; thioguanine), based on the experience in the two expert thiopurine centers in The Netherlands.

Meijer B, Mulder CJJ, van Bodegraven AA, de Boer NKH. How I treat my inflammatory bowel disease-patients with thiopurines? *World J Gastrointest Pharmacol Ther* 2016; 7(4): 524-530 Available from: URL: <http://www.wjgnet.com/2150-5349/full/v7/i4/524.htm> DOI: <http://dx.doi.org/10.4292/wjgpt.v7.i4.524>

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic condition of the gastrointestinal tract which is characterized by episodes of remission and relapses and encompasses both Crohn's disease (CD) and ulcerative colitis (UC). In the management of IBD, thiopurines [*i.e.*, azathioprine (AZA), mercaptopurine (MP) and thioguanine (TG)] play an important role in clinical practice, mainly in order to maintain remission^[1-4]. Over the past decades, extensive research has been performed to elucidate the complex metabolism of thiopurine derivatives^[5-7]. In this article, we demonstrate and discuss the way we use thiopurine therapy in the treatment of adult IBD patients in two referral centers in The Netherlands in daily practice. For information about thiopurine therapy in pediatric IBD, we refer to reviews focused on this patient group^[8-10].

DISCOVERY OF THIOPURINES

Thiopurines were firstly described in the early 1950s by Gertrude Elion and George Hitchings, primarily as antimetabolite therapy^[11]. Initially, thiopurines were used in the treatment of acute lymphatic leukemia in children and in the prevention of organ transplant rejection. The first IBD patient treated with thiopurines has been described by Dr. Bean^[12] in 1962. At this moment, thiopurines are used in a variety of autoimmune disorders and hematologic malignancies^[13,14].

PHARMACOLOGY OF THIOPURINES

The thiopurine derivatives AZA, MP and TG are all pro-drugs which are subsequently converted into the allegedly most important pharmacologically active end-metabolites, 6-thioguanine nucleotides (6-TGN)^[5]. AZA is converted into MP by the enzyme glutathione S-transferase, after which MP is metabolized by three competing enzymatic systems. First, a part of the concentration MP is withdrawn from bioavailability by xanthine oxidase (XO) and thiopurine-S-methyltransferase (TPMT), converting MP into 6-thiouric acid (6-TUA) and 6-methylmercaptopurine (6-MMP), respectively. The remaining concentration of MP is metabolized *via* the purine salvage pathway into 6-TGN by a cascade of hypoxanthine-guanine phosphoribosyl transferase (HGPRT), inosine monophosphate dehydrogenase (IMPD) and guanosine monophosphate synthetase (GMPS). The 6-TGN can be incorporated in the DNA (thus achieving an anti-metabolic effect), but also account for inhibition of anti-apoptotic effects and

down-regulation of pro-inflammatory cytokines. In daily practice, we measure 6-TGN and 6-MMP in red blood cells (RBC), which is mainly due to the fact that in patients with leukemia, the original indication for thiopurine therapy, successful treatment with thiopurines leads to the unavailability of leukocytes^[11,15].

In contrast to AZA and MP, the metabolism of TG is less extensive as TG is directly converted into 6-TGN by HGPRT. Whether TG is also withdrawn from bioavailability by the effect of TPMT and XO, this effect is relatively smaller than in AZA and MP, leaving a larger portion of TG available for (direct) conversion into 6-TGN (Figure 1)^[5,7,16,17].

INDICATIONS OF THIOPURINE THERAPY

When treating IBD patients in our centers, we apply the therapeutic approach known as accelerated step up care in both CD and UC^[18]. Conventional thiopurines (*i.e.*, AZA and MP) do not play a standard role in the active phase of CD and UC as such, however it may be added to induction course therapy with corticosteroids in those patients who are suspected of having a more severe or prolonged disease course. In patients with only mildly active disease with good reaction on initial induction therapy, thiopurines do not have to be initiated straight away^[19]. However, in those patients with a relapse of disease despite two induction courses of corticosteroids, thiopurines are required to maintain remission^[20]. Furthermore, thiopurines are co-administered as a routine to treatment with anti-TNF therapy in our centers, in line with recent observations from the SONIC trial^[2-4,21]. In those patients receiving vedolizumab (Entyvio®) evidence is scarce whether to (dis)continue simultaneous thiopurine therapy^[22,23]. In our centers, we continue thiopurine therapy in the majority of patients, since patients receiving vedolizumab are likely to have highly complex disease in which vedolizumab is often initiated as rescue drug. Additionally, in line with the observations in the SONIC trial in patients receiving infliximab and adalimumab, we presume that thiopurines might have a protecting effect on the development of antibodies against vedolizumab^[24,25]. Finally, thiopurines are administered in surgical CD patients to prevent post-surgical recurrence, especially in complex patients with fistulizing disease or multiple surgical interventions^[3].

Thiopurine therapy is initiated in a dosage of 2.0-2.5 mg/kg for AZA or 1.0-1.5 mg/kg for MP, starting with 50 mg/d in the first week and increasing to full-dose when patients experience no adverse effects on low-dose therapy^[1]. In those patients in whom thiopurines were co-administered next to induction corticosteroid therapy, the steroids are tapered down in 2-3 mo.

In our center, we prefer to initiate thiopurine therapy using MP, based on results of several rechallenge studies^[26-31]. Furthermore, in those patients with mild adverse events (*i.e.*, no severe myelotoxicity or pancreatitis) on MP therapy, we rechallenge these patients with MP with low threshold.

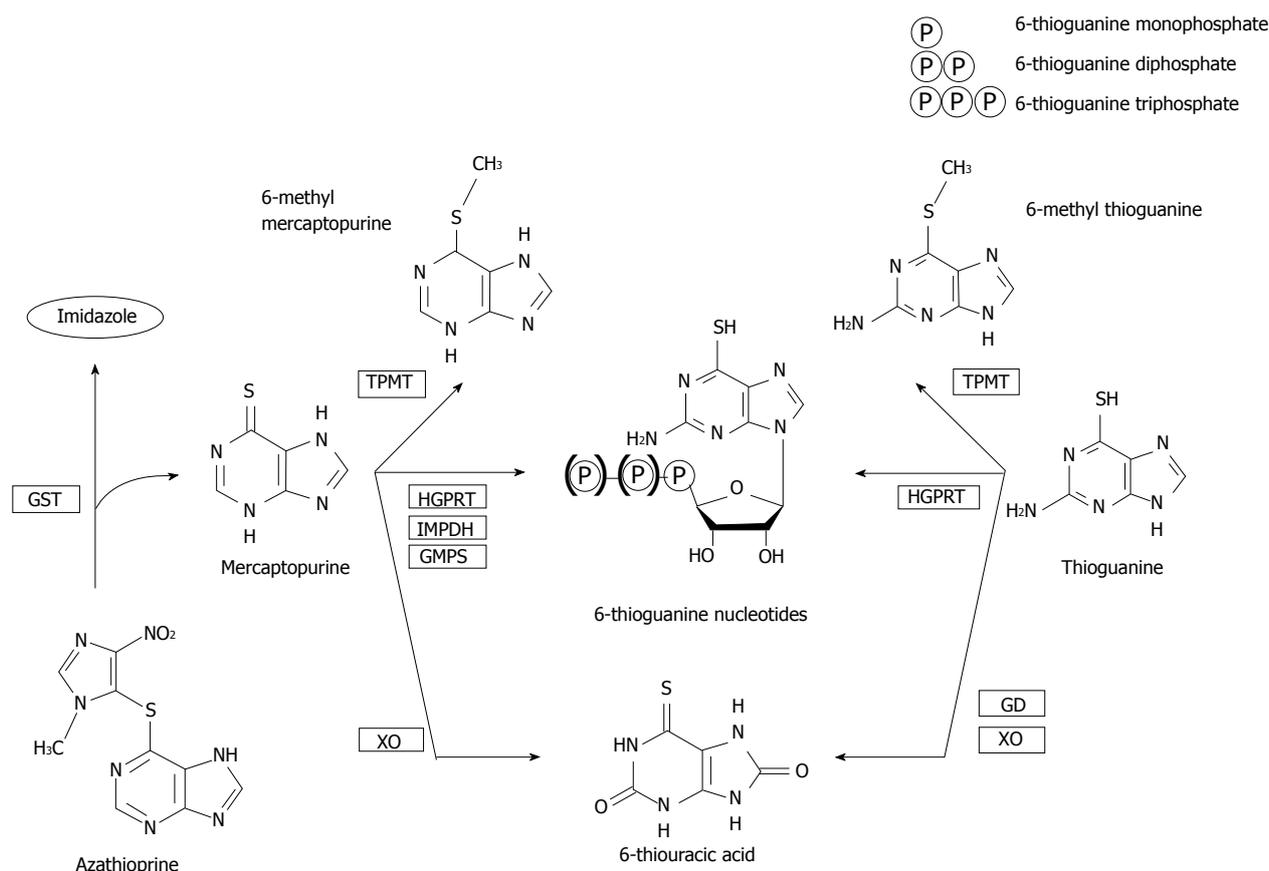


Figure 1 Simplified scheme of thiopurine metabolism. Azathioprine is converted to mercaptopurine by the enzyme glutathione S-transferase (GST), by separating the imidazole-group. 6-Mercaptopurine is enzymatically converted into 6-methylmercaptopurine (6-MMP) by thiopurine-S-methyltransferase (TPMT) and into 6-thiouracilic acid (6-TUA) by xanthine oxidase (XO). The remaining portion of mercaptopurine is converted into the biochemically active end-metabolites 6-thioguaninenucleotides (6-TGN, consisting of 6-thioguanine monophosphate, 6-thioguanine diphosphate and 6-thioguanine triphosphate) by a pathway of hypoxanthine-guanine phosphoribosyl transferase (HGPRT), inosine monophosphate dehydrogenase (IMPDH) and guanosine monophosphate synthetase (GMPS). Thioguanine is metabolized by TPMT into 6-methylthioguanine (6-MTG) and into 6-TUA by guanine deaminase (GD) and XO. The remaining portion of thioguanine is directly converted into 6-TGN by HGPRT. Squared abbreviations display enzymatic conversions. Adapted from van Asseldonk *et al.*^[6].

TOXICITY OF THIOPURINE THERAPY

As thiopurines are associated with a broad spectrum of adverse events (*i.e.*, flu-like symptoms, arthralgia, gastrointestinal complaints, rash, pancreatitis, hepatotoxicity and myelotoxicity), one of the applied strategies to reduce the risk of developing adverse events is to measure TPMT activity before initiating thiopurine therapy, to identify patients at risk of developing adverse events based on an aberrant thiopurine metabolism^[7,16,32,33]. Literature reports show that 1:300 (Caucasian) individuals have TPMT deficiency, making them at risk for developing (severe) myelosuppression due to preferential 6-TGN formation^[34]. In our centers, however, TPMT activity is not determined as we initiate thiopurine therapy with a low-dose start up scheme. Furthermore, many patients with normal TPMT activity could still develop adverse events of thiopurine therapy^[32,35,36]. For this reason amongst others, we choose to extensively monitor laboratory and clinical parameters in the first three months after initiation of thiopurine therapy. At week 0, 1, 2, 4, 8 and 12, hematologic and hepatic parameters are being measured, as well as creatinine and C-reactive protein (Table 1). After initiation, these parameters are determined each 3-4 mo during

Table 1 Laboratory tests to determine risk of myelotoxicity and hepatotoxicity during initiation of thiopurine therapy

Hematologic parameters
Hemoglobin
White blood cell count
Platelet count
Hepatic parameters
Alkaline phosphatase
Gamma glutamyl transpeptidase
Alanine aminotransferase
Other parameters
Creatinine
C-reactive protein

Measuring of above mentioned parameters: Induction phase: week 0, 1, 2, 4, 8 and 12; Maintenance phase: Each 3-4 mo.

thiopurine maintenance therapy.

MEASURING METABOLITES

Measurement of thiopurine metabolites (6-TGN and 6-MMP) is not performed routinely in clinical practice at our centers. In those patients who experience adverse

Table 2 Interpretation of metabolite levels in patients with inflammatory bowel disease treated with azathioprine or mercaptopurine

6-TGN (pmol/8 × 10 ⁸ RBC)	6-MMP (pmol/8 × 10 ⁸ RBC)	Non-response	Adverse event (dose-dependent)	Recommendation
<< 230	<< 5700	Non-compliance	Not expected	Gain compliance
< 230	< 5700	Non-compliance/under dosing	Not expected	Gain compliance/increase dose ¹
230-400	< 5700	Possible resistance to thiopurine therapy	Not expected	Increase dose ¹ or change therapy ²
> 400	< 5700	Therapy resistance	Myelotoxicity	Change therapy ²
< 230	>> 5700	Shunting	Myelotoxicity	Consider allopurinol ³ or switch to TG ⁴
< 230	> 5700	Shunting	Hepatotoxicity	Consider allopurinol, 5-ASA or switch to TG
230-400	> 5700	Possible resistance to thiopurine therapy	Hepatotoxicity	Consider allopurinol ³ or 5-ASA
> 400	> 5700	Therapy resistance	Hepatotoxicity	Change therapy ²
			Myelotoxicity	Decrease dose ⁵

Therapeutic target of therapy: 6-TGN: 230-400 pmol/8 × 10⁸ RBC; 6-MMP: < 5700 pmol/8 × 10⁸ RBC. ¹AZA: Increase with 50 mg, MP: Increase with 25 mg; ²In case of thiopurine refractoriness, consider switch of therapy to non-thiopurine therapy; ³Allopurinol co-treatment with 100 mg daily requires dose-adjustment of thiopurine therapy to approximately 25%-33% of original daily dose^[38,60]; ⁴Treatment with thioguanine in low dose (*i.e.*, 0.3 mg/kg) bypasses the formation of 6-MMP; ⁵In case of adverse events. 6-TGN: 6-thioguanine nucleotides; 6-MMP: 6-methylmercaptopurine; RBC: Red blood cells; <: Lower than; <<: Much lower than; >: Higher than; >>: Much higher than; AZA: Azathioprine; MP: Mercaptopurine; TG: Thioguanine; 5-ASA: 5-aminosalicylic acid (mesalazine).

events or non-response to treatment, metabolite levels may explain why these patients are intolerant or resistant to therapy (Table 2). Based on these results, individual treatment strategies (*i.e.*, split-dose administration, dose reduction/increase, the addition of mesalazine or allopurinol to a 25%-33% dose of the original thiopurine in patients with an altered thiopurine metabolism, so-called "skewers") may be applied^[37-39].

TG THERAPY

In those patients with either idiosyncratic (*e.g.*, pancreatitis) adverse events on conventional thiopurine therapy or adverse events based on elevated 6-MMP concentrations, these patients can be switched to TG. In some countries, TG is considered as rescue drug when conventional therapy fails, however, in The Netherlands this drug is officially registered as treatment option for IBD since March 2016. One of the feared complications of TG treatment is the development of nodular regenerative hyperplasia (NRH), a condition of the liver in which patients might develop non-cirrhotic portal hypertension. However, in contrary to earlier observations^[40-42], the development of NRH is seldomly witnessed in those patients treated with low-dose TG therapy (*i.e.*, 0.3 mg/kg)^[43-47] and furthermore not associated with clinically relevant liver disease^[48]. In our patients treated with TG, liver biopsies are only performed in patients with symptoms of portal hypertension or persisting liver test abnormalities and no longer as a routine^[48].

CANCER RISK

The use of thiopurines is associated with a three- to fivefold higher risk of the development of lymphoproliferative disorders, in particular non-Hodgkin lymphoma, as well as hepatosplenic T-cell lymphoma, especially in patients without prior Epstein-Barr virus (EBV) exposure^[49]. We do not systematically test EBV

seroprevalence in patients starting with thiopurines, since over 90% of Dutch inhabitants are exposed to EBV during childhood^[50].

Furthermore, there is a clinically significant elevated risk of developing non-melanoma skin cancer, such as squamous cell carcinoma and basal cell carcinoma^[49,51]. In our centers, we inform our patients of this higher risk and instruct them to, for example, apply sunscreen to unprotected skin and mention newly developed skin lesions directly to the treating physician or IBD-nurse. However, since the absolute incidence of these malignancies in thiopurine-using IBD patients is still low, we do not systematically screen our patients for the existence of these tumors.

PREGNANCY

According to recent literature reviews, conventional thiopurine use during pregnancy is not associated with a higher risk of preterm birth, congenital disorders or children with low birth weight^[52-54]. For this reason amongst others, we do not cessate thiopurine therapy in patients that become pregnant, but we refer patients during pregnancy to a dedicated team of gynecologists with interest in IBD. Furthermore, after a successful pregnancy, there is insufficient evidence to discourage patients to give breastfeeding; however, this should always be adjusted to the individual patient wishes^[55-57]. Evidence concerning the use of TG during pregnancy is scarce and further prospective trials are needed to confirm the safety of this thiopurine derivative in pregnant women^[58].

WHEN TO STOP THIOPURINE THERAPY?

Whether patients achieving a deep remission may successfully stop thiopurines is not known^[19,59,60]. In our centers, we continue thiopurine therapy with low threshold, especially in patients with a predicted complex

course (*i.e.*, severe or difficult to manage disease). An exception is the patient with deep prolonged (*i.e.*, ≥ 2 -3 years) remission on thiopurine therapy with no signs of active disease on clinical, biochemical, endoscopic, histological and radiologic evaluation. In these patients, thiopurine therapy could be ceased with a good probability of relapse-free disease.

CONCLUSION

Whereas treatment with thiopurine therapy in IBD patients is hampered by a high number of discontinuations, mostly due to adverse events, several treatment strategies may be applied to maximize effectiveness and optimize safety. With this article, we provided a practical overview on how thiopurine therapy is being prescribed in two of the thiopurine research expert centers in Europe. We provided information concerning pharmacotherapy, indications of thiopurine treatment, toxicity of thiopurines and how to optimize treatment in individual patients using different treatment strategies.

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P- Reviewer: Actis GC, Capasso R, Serban DE **S- Editor:** Ji FF
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