REVIEWS

Dosing 6-Thioguanine in Inflammatory Bowel Disease: Expert-Based Guidelines for Daily Practice

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Abstract

Conventional thiopurines are considered to be effective and safe in the treatment of inflammatory bowel disease (IBD) patients; unfortunately more than 50% of patients discontinue thiopurine therapy, mainly due to the development of intractable adverse events. In recent years, the use of 6-thioguanine has been proposed as an alternative thiopurine in IBD patients failing to tolerate or to respond to conventional thiopurine therapy. In this clinical review, we describe the rationale for 6-thioguanine therapy and discuss the reported hepatotoxicity of 6-thioguanine (especially nodular regenerative hyperplasia). We propose expert-based guidelines for balanced treatment.

Key words

6-thioguanine – Crohn's disease – ulcerative colitis – thiopurines – side-effects – nodular regenerative hyperplasia – guidelines.

Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are characterized by a chronic intestinal inflammation with a relapsing clinical course. Maintenance therapy is for that reason often indicated. In CD, conventional thiopurines - azathioprine (AZA) and 6-mercaptopurine (6-MP) - are considered maintenance drugs of choice for steroid-dependent and steroid-refractory disease, whenever indicated (according to current ECCO - guidelines). Thiopurines are considered to be effective and well tolerated. Unfortunately, more than 50% of patients discontinue thiopurine therapy, mainly due to the development of adverse events [1].

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Methotrexate (MTX) is also effective for this maintenance indication in CD patients, at least in patients in whom remission has been achieved by this immunosuppressive agent [2]. Regular infusions of infliximab (IFX) or adalimumab (ADA) subcutaneously may be considered as a maintenance option in CD patients who are refractory or intolerant to conventional thiopurines or MTX. However, in the case of IFX - use, concomitant immunosuppression with thiopurines or MTX is recommended to minimize the immunogenicity. In addition, conventional thiopurines offer an inexpensive treatment option in comparison with biologic therapies: IFX and ADA are about 30-40 times more expensive as compared with AZA and 6-MP. In UC, 5-aminosalicylates (5-ASA) are the drugs of choice to induce and, subsequently, maintain remission. In case of intolerance or drug resistance, AZA and/or 6-MP may be administered for maintenance of remission and steroid-sparing, respectively.

In recent years, the use of 6-thioguanine (6-TG) has been proposed as an alternative for AZA and 6-MP in IBD patients failing to tolerate or to respond to conventional thiopurine therapy. In this clinical review, we describe the rationale for 6-TG therapy and discuss its hepatotoxic profile, with a special focus on nodular regenerative hyperplasia of the liver. In addition, we propose expert-based guidelines for balanced treatment with 6-TG.

Rationale for 6-thioguanine therapy

Most of the clinical and pharmacological data on 6-TG stems from studies in haematological malignancies. In IBD, treatment with 6-TG was described as early as 1966 in three UC patients. Therapy was discontinued prematurely in all three patients due to the development of adverse events. In more recent years, 6-TG has been considered as an alternative treatment option in IBD patients who failed to continue therapy with conventional thiopurines due to intolerance or refractoriness.

Theoretically, 6-TG has several potential metabolic advantages when compared to AZA and 6-MP. The first metabolic difference of 6-TG is its direct conversion into

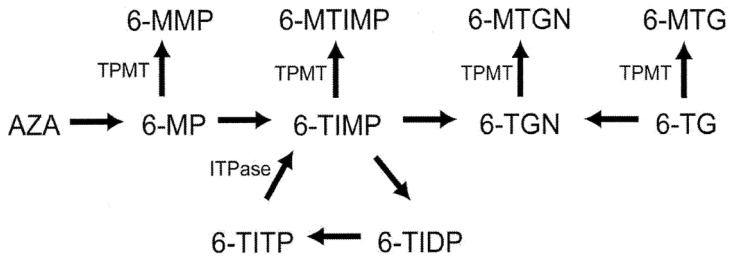

Fig 1. Simplified thiopurine metabolism scheme adapted from reference 15. Azathioprine (AZA) is degraded to 6-mercaptopurine (6-MP). Thiopurine methyl transferase (TPMT) methylates 6-MP into 6-methylmercaptopurine (6-MMP). By hypoxanthine guanine phosphoribosyl transferase, 6-MP is catalyzed to 6-thioinosine-monophosphate (6-TIMP). Via two other (including hypoxanthine guanine phosphoribosyl transferase) enzymatic steps the 6-thioguaninenucleotides (6-TGN) are ultimately generated. 6-TIMP and 6-TGN may also be methylated by TPMT leading to 6-methyl-thioinosine-monophosphate and 6-methylthioguaninenucleotides (6-MTGN), respectively. In a cycle 6-TIMP is phosphorylated to 6-thioinosine-diphosphate (6-TIDP), subsequently to 6-thioinosine-triphosphate (6-TITP) and ultimately back to 6-TIMP due to the inosine triphosphate pyrophosphatase (ITPase). When ITPase activity is impaired or lacking, 6-TITP accumulates. 6-Thioguanine (6-TG) is directly converted in 6-TGN but may also be methylated by TPMT leading to 6-methylthioguanine (6-MTG).

the pharmacologically active 6-thioguanine nucleotides (6-TGN) (Fig. 1). As compared to the metabolisation of conventional thiopurines, the number of enzymatic steps to generate the alleged pharmacologically active metabolite is limited.

The methylating enzyme thiopurine methyltransferase (TPMT) plays a critical role in the metabolism of the conventional thiopurines. High TPMT activity will result in high concentrations of the metabolites 6-methylmercaptopurine ribonucleotides, which have been associated with 6-MP resistance and hepatotoxicity. Low or absent activity will result in (extremely) elevated levels of 6-TGN which may lead to myelotoxicity. It is believed that TPMT has a less central role in the metabolisation of 6-TG, hence induction of hepatotoxicity and myelotoxicity may be limited [3].

During AZA and 6-MP treatment, diminished activity of the enzyme inosine triphosphate pyrophosphohydrolase (ITPase) is associated with the development of flu-like symptoms, rash and pancreatitis, whereas ITPase is not involved in 6-TG metabolism [4].

In conclusion, the apparent metabolic advantages of 6-TG compared to the conventional thiopurines are the more direct conversion into 6-TGN, the limited influence of the enzyme TPMT, the lack of influence of the enzyme ITPase and the absence of potential toxicity from 6-MMPR.

Hepatotoxicity of 6-thioguanine

Initial short-term reports on the toxicity profile of 6-TG were comforting [5, 6]. In 2003, however, Dubinsky et al reported a prevalence of nodular regenerative hyperplasia (NRH) in 16 out of 26 (62%) biopsies taken from 111 IBD patients treated with 6-TG [5]. The authors concluded that this serious complication was idiosyncratic and that 6-TG should no longer be considered as a therapeutic option in IBD patients since data on progression to (complicated) non-cirrhotic portal hypertension or, alternatively, reversibility of NRH were lacking. It has to be stated that in this study, however, most patients were pre-treated with AZA or 6-MP, and 40% had signs of hepatotoxicity during this preceding therapy. Moreover, the dosage of 6-TG administered in this study was not reported accurately, whilst the observed median 6-TGN level was approximately 1250 pmol/8x10^8 RBC. As a response, several other research groups published their data on 6-TG therapy and the prevalence of NRH (Table I). These subsequent studies appeared to show a dose-dependent NRH effect with no or only few cases of NRH (0-4%) observed in the patient groups treated with

Table I. Nodular regenerative hyperplasia of the liver during 6-thioguanine therapy

Dosage of 6-TG	6-TGN level	Observed NRH	Reference
unknown	1230 (530-2310)	62% (16/26)	[21]
20 mg/day	564 (SD 278)	0% (0/28)	[6]
20 mg/day	802 (106-1092)	0% (0/13)	[7]
20 - 40 mg/day	unknown	27% (16/60)	[11]
0.28 mg/kg/day	unknown	4% (7/99)	[8]
40 mg/day	807 (105-2545)	0% (0/11)	[9]
40 - 80 mg/day	unknown	18% (8/45)	[10]

Abbreviations: 6-TG = 6-thioguanine; 6-TGN = 6-thioguanine nucleotides (expressed in pmol/8x10^8 RBC), presented as median with range or mean with standard deviation (SD); NRH = nodular regenerative hyperplasia.

a maximum daily dose of 24 mg 6-TG [6-8]. In patients treated with reported higher dosages (40 to 80mg per day), NRH was observed in 0 to 27% of liver biopsies [9-11]. The disturbingly high prevalence rate of NRH of 62% was not observed in any other study.

De Boer et al demonstrated a background prevalence of 6% of NRH in thiopurine naïve operated IBD patients and a significant correlation between NRH and age at biopsy (p=0.015) [12]. Therapy with the conventional thiopurines has also been associated with the development of NRH, induction of NRH might be a drug-class effect (related to thiopurines in general), instead of solely a dose related 6-TG effect.

The reversibility of NRH and its potential complications have been studied by the measurement of the hepatic venous pressure gradient. It was demonstrated that discontinuation of 6-TG therapy attenuates portal hypertension reducing the risk from these complications [13]. Further studies are necessary to investigate whether early-stage NRH induced portal hypertension may be, in part, reversible after the cessation of therapy.

Proposed expert-based guidelines on safety monitoring

In 2004, an European 6-TG working party formulated the following expert-based guidelines for future 6-TG administration [14]: 6-TG may be considered in IBD patients with a requirement for maintenance therapy as well as intolerance and/or resistance to 5-aminosalicylates (in UC), AZA, 6-MP and MTX (in CD) and without an appropriate option for surgery. Therapy with biologics may be considered as a maintenance option in CD and UC before applying 6-TG. However, only 30-40 % of the UC patients treated with biologics therapy were in remission after 12 months [15].

Based on the recent published data, we recommend the following practices. Written informed consent should be obtained from the patient after providing adequate information on its (hepato)toxic profile, especially as IBD is an off-label indication of 6-TG. It is recommended that 6-TG administration should be started at a dosage of approximately 20 mg per day and should not exceed 25 mg daily. Safety monitoring is of pivotal significance during 6-TG therapy and must be performed on a regular basis in all patients (Table II). The drug has to be withdrawn in case of a twofold rise of at least one liver test if at least possibly related to 6-TG use. The 6-TG dose should be reduced when leukocyte counts are between 1.0 and 3.5 x 10^9/l and administration has to be discontinued when the leukocyte count is lower than 1 x 10^9/l. In patients with a low platelet count (<150 x 10^9/l) we recommend to perform a liver biopsy, as low platelets counts have been associated with NRH and portal hypertension.

Current monitoring still includes histological evaluation of the liver specimen after one, three and, then after every three years of 6-TG treatment. Staining with haematoxylin and eosin (H&E), (silver)reticuline and trichrome are mandatory [16]. If histological abnormalities consistent with NRH are found in the specimens the treatment of 6-TG should be discontinued. Therapeutic drug monitoring (measuring 6-TGN levels in erythrocytes) is of limited value during 6-TG therapy; however, it might help to interpret the occurrence of some adverse events. For determination of drug compliance measurement of 6-TGN will remain the gold standard.

Table II. Drug monitoring of 6-TG

Parameters	At which moment ?
Complete blood count	Baseline, 1, 2, 4, 8 and 12 weeks. Every 3 months
Hemoglobin	Baseline, 1, 2, 4, 8 and 12 weeks. Every 3 months
6-thioguanine nucleotides	Optional to check patient compliance
Alanine aminotranferase	Baseline, 1, 2, 4, 8 and 12 weeks. Every 3 months
Aspartate aminotransferase	Baseline, 1, 2, 4, 8 and 12 weeks. Every 3 months
Alkaline phosphatase	Baseline, 1, 2, 4, 8 and 12 weeks. Every 3 months
Gamma-glutamyl transferase	Baseline, 1, 2, 4, 8 and 12 weeks. Every 3 months
Bilirubin	Baseline, 1, 2, 4, 8 and 12 weeks. Every 3 months
Liver biopsy	After 1 and 3 year and then every 3 years
C-reactive protein (efficacy control)	Baseline, 1, 2, 4, 8 and 12 weeks. Every 3 months

Contradictory results have been published in case reports regarding the potential teratogenic effects of 6-TG in leukaemia patients [17, 18]. Two cases have been published about 6-TG therapy in CD patients during pregnancy, which demonstrated no teratogenic effects [19]. Further studies are required to determine how safe the use of 6-TG is during pregnancy or lactation in IBD patients. For that reason, 6-TG should be avoided during pregnancy or lactation.

Dosing of 6-Thioguanine

Formal dose-ranging studies are lacking and only limited data are available on therapeutic efficacy and dosing regimes. In The Netherlands, a dosage of approximately 0.3 mg/kg bodyweight per day is prescribed, hence, usually around 20 mg. As a general rule, dosage should not exceed 25 mg daily, as higher dosing of 6-TG has been associated with an increased risk of developing NRH. This dosing regime has been demonstrated to be tolerated by 79 % of IBD patients, who were intolerant for the preceding conventional thiopurines [20].

Conclusion

6-Thioguanine can be considered a rescue drug in IBD patients intolerant of or refractory to the conventional thiopurines and/or methotrexate. The reported incidence of NRH related to 6-TG use is of general concern but may well

be comparable with conventional thiopurine use. Moreover, IBD itself should probably be considered as a risk factor to develop NRH. Nevertheless, a rigorous monitoring including regular liver biopsies is advocated.

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