REVIEW

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Thioguanine Therapy in Inflammatory Bowel Diseases. A Practical Guide

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ABSTRACT

Thiopurine-derivates azathioprine and mercaptopurine are frequently used to maintain remission in inflammatory bowel diseases (IBD). Despite their efficacy, more than 50% of patients discontinue therapy, mainly due to the development of adverse events. Thioguanine is an alternative thiopurine and has been conditionally licensed in The Netherlands as IBD treatment for patients after conventional thiopurine therapy failure. In this review we will provide practical information on initiating and maintaining thioguanine therapy in IBD and provide information concerning safety issues and future perspectives. The thioguanine toxicity profile is relatively mild and the reported incidence of nodular regenerative hyperplasia related to thioguanine use seems comparable to conventional thiopurines and the background incidence in IBD patients. Routine monitoring of laboratory parameters and adverse events is recommended, comparable to the monitoring of patients on conventional thiopurine therapy.

Key words: inflammatory bowel diseases – thioguanine – guideline – drug-related side effects and adverse reactions.

Abbreviations: AZA: azathioprine CD: Crohn's disease; EBV: Epstein-Barr Virus; HGPRT: hypoxanthine-guanine phosphoribosyl transferase; HLH: hemophagocytic lymphohistiocytosis; HR: hazard ratio; IBD: inflammatory bowel diseases; ITPase: inosine triphosphate pyrophosphohydrolase; MP: mercaptopurine; NRH: nodular regenerative hyperplasia; OR: odds ratio; TDM: therapeutic drug monitoring; TG: thioguanine; TNF: tumor necrosis factor; TPMT: thiopurine methyltransferase; UC: ulcerative colitis; WBC: white blood cell count; XO: xanthine oxidase; 5-ASA: 5-aminosalicylates; 6-thio-ITP: 6-thiosine triphosphate; 6-MMP: 6-methylmercaptopurines; 6-TGN: 6-thioguanine nucleotides.

INTRODUCTION

Given the relapsing clinical course of Crohn's disease (CD) and ulcerative colitis (UC), together known as inflammatory bowel diseases (IBD), maintenance therapy is commonly needed to maintain remission. There are various drugs used for this reason including conventional thiopurines as azathioprine (AZA) and mercaptopurine (MP) [1, 2]. Despite their effectiveness, 50% of patients discontinue thiopurine therapy, mainly due to the development of adverse events [3]. When adverse effects develop or therapy fails for another reason, an option may be switching to a third thiopurine-derivate: thioguanine (TG).

This practical review is an update of our earlier proposed expert based guideline in 2010 as larger studies have become available in this field since then [4]. Moreover, TG received a conditional license for the treatment of IBD in the Netherlands in 2015 and can be prescribed to patients who previously failed conventional thiopurine therapy due to a lack of response or adverse effects [5].

METABOLISM OF THIOGUANINE

Due to a different metabolic pathway, theoretically, TG has potential advantages as compared to MP or AZA. One of the main differences is the direct conversion into the pharmacological active 6-thioguanine nucleotides (6-TGN) by hypoxanthine-guanine phosphoribosyl transferase (HGPRT) without the formation of potential hepatotoxic 6-methylmercaptopurines (6-MMP) (Fig. 1) [6]. Another difference is the less central role

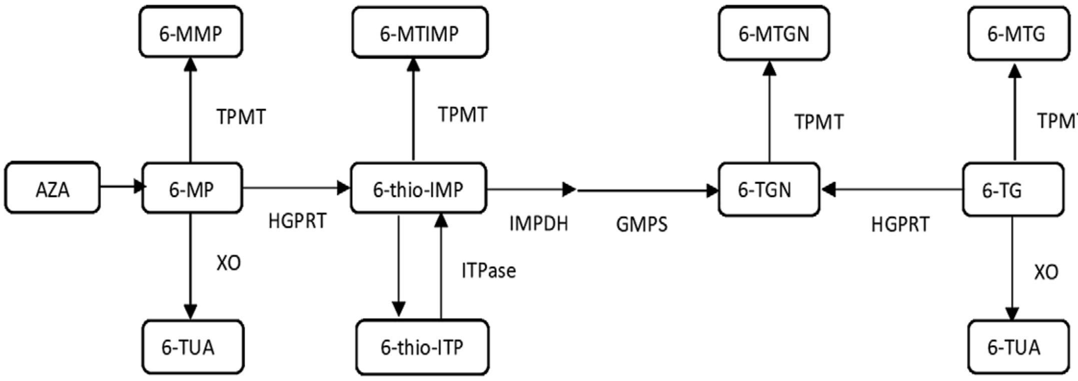

Fig. 1. Simplified thiopurine metabolism scheme. Azathioprine (AZA) is converted to 6-mercaptopurine (6-MP). Thiopurine methyltransferase (TPMT) methylates 6-MP into the potential hepatotoxic 6-methylmercaptopurine (6-MMP) and xanthine oxidase (XO) can catabolize 6-MP into 6-thiouric acid (6-TUA). Hypoxanthine-guanine phosphoribosyl transferase (HGPRT) converts 6-MP into 6-thiosine monophosphate (6-thio-IMP). 6-thio-IMP can be further metabolized into the active 6-TGN. 6-TGN may also be methylated by TPMT leading to 6-methylthioguanine nucleotides (6-MTGN). In a cycle 6-tio-IMP is eventually phosphorylated to 6-thiosine triphosphate (6-thio-ITP) and ultimately back to 6-thio-IMP due to inosine triphosphate pyrophosphatase (ITPase). 6-thioguanine (6-TG) is directly converted into 6-TGN but may also be methylated by TPMT into 6-methylthioguanine (6-MTG) or catabolized into 6-TUA by XO.

of thiopurine methyltransferase (TPMT) in the metabolism of TG, in contrast to the importance of this enzyme in the metabolism of AZA and MP. Unfortunately, patients treated with AZA or MP can have a preferential shunting towards 6-MMP or 6-TGN formation depending on the activity of TPMT [7, 8]. Although TG can also be converted by TPMT or xanthine oxidase (XO), this effect is limited compared with conventional thiopurines, resulting in a larger amount of TG available for conversion into 6-TGN. During conventional thiopurine therapy, diminished activity of the enzyme inosine triphosphate pyrophosphohydrolase (ITPase) has been associated with the development of adverse events such as rash, pancreatitis and flu-like illness possibly due to an accumulation of 6-thiosine triphosphate (6-thio-ITP) [9]. TG is not a substrate for ITPase, therefore this metabolic step is bypassed and 6-thio-ITP does not accumulate in ITPase deficient patients [9].

In summary, the apparent metabolic advantages of TG compared to AZA or MP are the more direct conversion into 6-TGN without potentially rate limiting steps, less influence of the enzyme TPMT, the absence of formation of potential hepatotoxic 6-MMP, less side metabolites in general and no side-effects induced by ITPase.

CONVENTIONAL THIOPURINES AND THIOGUANINE THERAPY

Conventional thiopurines, AZA or MP, are in general not prescribed as induction therapy in the active phase of CD or UC, but if a more severe disease course is expected they can be co-administrated together with an induction course of corticosteroids. However, in steroid-dependent CD they are prescribed as maintenance drugs of choice [1]. 5-aminosalicylates (5-ASA) are the primary drugs of choice to induce and maintain remission in UC. In case of intolerance or drug resistance, thiopurines may be administered for maintenance of remission and steroid sparing, respectively [2]. In addition to their role as first-line immunomodulators, thiopurines are also prescribed in combination with anti-tumor necrosis factor (anti-TNF), especially infliximab, to induce and maintain remission in patients with an inadequate response to conventional therapy, resulting in higher rates of clinical remission and better mucosal healing [1, 10]. Besides the higher rates of clinical remission with combination therapy, the randomized control SONIC trial among biological and immune modulator naïve CD patients also demonstrated that less patients developed antibodies in the combination therapy group compared to patients with monotherapy infliximab (0.9% vs 14.6%) and there was a significantly lower median through level of serum infliximab in the latter [10]. Also, in patients previously treated with an anti-TNF, not only in those who experience immune-mediated loss of response, thiopurines or methotrexate may be used in combination with the prescribed second anti-TNF [11]. There are studies which suggest that patients who have a loss of response on monotherapy thiopurines do not benefit from the continuation of thiopurines once biologic therapy is begun, although hard evidence is lacking and lower immunogenicity should also be considered in these patients [1, 12, 13]. In the short-term, combination therapy seems safe since the SONIC trial showed that there was no significant difference with regard to serious adverse events or infection after 1 year combination therapy. In the long-term however, there seems to be an increased risk of opportunistic [Hazard ratio (HR), 1.96] and serious (HR, 1.23) infections compared with monotherapy anti-TNF [14]. In addition, a case-control study showed that the use of two or more immunosuppresants (corticosteroids, AZA/MP or infliximab) gives an odds ratio (OR) of 14.5 for opportunistic infections compared with an OR of 2.9 for monotherapy [15]. So, in clinical practice the added benefits of combination therapy should always be balanced against the potential increase in adverse events. There is no added value of combining vedolizumab, ustekinumab and tofacitinib with a thiopurine [16].

When initiating a thiopurine the use of MP may be preferred as initial therapy rather than AZA, based on several rechallenge studies [17-19]. These studies showed that up to 68% of patients intolerant to AZA were able to tolerate MP [17-19]. If therapy with a conventional thiopurine fails or adverse effects develop, management can include dose reduction, combining low dose thiopurine with allopurinol and assessing metabolite levels [i.e. therapeutic drug monitoring (TDM): measuring 6-TGN and 6-MMP levels in erythrocytes)] or switching to the alternative thiopurine TG.

When patients experience side-effects related to elevated 6-MMP levels, we discuss two possible strategies: to start with the combination azathioprine/allopurinol therapy or to switch to monotherapy TG. Due to the lower pill burden the latter is often preferred [20]. Also, patients who still experience mild side-effects after a rechallenge with MP can benefit from a switch to TG [21, 22]. Side effects during TG therapy tend to be different than those experienced with AZA or MP and patients intolerant to conventional thiopurines uncommonly have recurrence of these adverse effects with TG [21, 22]. A key setting in which it is recommended to switch to TG therapy is a history of pancreatitis during conventional thiopurine therapy, as multiple studies have demonstrated that previous thiopurine-induced pancreatitis did not reoccur with TG treatment [21, 23].

EFFECTIVENESS AND LONG-TERM SAFETY OF THIOGUANINE

Since TG is a commonly used drug in the treatment of acute nonlymphocytic leukemia and acute lymphoblastic leukemia and approved by the EMA (European Medicines Agency) and the FDA (Food and Drug Administration) for this intent, it is available in most countries as off-label IBD treatment. Moreover, in the Netherlands, TG (Thiosix® 10 and 20 mg tablets) has been conditionally licensed as a certified IBD treatment since 2015 for patients who previously failed conventional thiopurine therapy due to lack of response or adverse effects [5]. Besides the Netherlands more national guidelines, for example the guideline of New Zealand, mentioned TG as an alternative for conventional thiopurines, even though it is not brought up in international IBD guidelines.

A systematic review about the efficacy of TG treatment after AZA/MP failure showed clinical improvement, defined as a decrease in symptoms scales or the opportunity to cease or clinically significantly decrease corticosteroids without disease relapse, in 65% [24]. Almost all patients in the included studies were treated with monotherapy TG or used TG in combination with steroids, cyclosporine or 5-ASA (5-aminosalicylic acid); only 18 out of 353 included patients were treated with combination therapy. The effectiveness found in this systematic review roughly corresponds to available literature regarding the efficacy of AZA or MP, despite most included patients experienced intolerance or inadequate response to previous AZA or MP therapy [24-26]. The type of IBD seems to have no influence on the effectiveness of TG. Studies revealed no significant difference in the response rate between CD and UC patients and both patient groups benefited from therapy with TG [24, 27].

The long-term safety of TG therapy was investigated in a retrospective study by Simsek et al. [27]. This study included 274 IBD patients who previously failed therapy with conventional thiopurines and were now treated with a median dosage of 20 mg TG. This study demonstrated a median duration of TG use of 51 months (IQR: 36-89) with 1,567 patient-years of follow up [27]. In this retrospective cohort 112 patients (41%) reported a total of 186 adverse events during 1,567 patient-years of follow-up and the majority (65%) of adverse events was graded as mild according to the CTCEA. Intolerable severe adverse events leading to withdrawal of therapy were reported in 11%, mainly in patients who recently started TG therapy [27]. In addition, a smaller retrospective study, which included 54 IBD patients who also failed previous therapy with conventional thiopurines, concluded that the efficacy and side-effects of TG [mean dose 27 mg/d (range 20-40 mg/d)] were comparable to AZA/MP and that the safety data are reassuring [21]. Although longer follow-up safety data for conventional thiopurines are available and both drugs have never been head-to-head compared, it appears that these data are, to some extent, comparable. It must be said, however, that all patients in the retrospective TG cohort previously failed conventional thiopurines [21, 27].

The effectiveness of combination therapy with anti-TNF and TG, instead of AZA/MP, is not yet determined. One could speculate that TG has the same effect on immunogenicity as AZA/MP, certainly since methotrexate (another immune modulator) demonstrated similar effects of decreasing antibodies to infliximab and increasing infliximab trough levels, but firm evidence is lacking [28].

DOSING, INITIATION AND FOLLOW-UP OF THIOGUANINE THERAPY

Formal large dose-ranging studies are lacking, but in the Netherlands a dosage of approximately 0.2-0.3 mg/kg bodyweight per day is prescribed, leading to a standard dosage of 20 mg per day. This dosing regime is tolerated by up to 80% of patients who were intolerant for preceding conventional thiopurines [24]. Moreover, a systematic review demonstrated that the two studies with a starting dose of 20 mg per day had the highest effectiveness rate, possibly because a lower dosage leads to better tolerability and could therefore contribute to longer usage and subsequent higher efficacy [24]. It is recommended that the dosage should not exceed 25 mg per day since a higher dosage has been associated with an increased risk of drug-induced liver injury, especially nodular regenerative hyperplasia (NRH) [29-35].

Thioguanine seems to have a clinically faster onset of action than AZA/MP and there are studies which demonstrated that some patients have a clinical response after 4 weeks [36, 37]. However, just as with AZA/MP, sometimes it can take multiple weeks or months before treatment with TG is effective, making it less suitable for induction of response.

In general, before prescribing a thiopurine (AZA, MP or TG), the immunization status against certain infections (e.g. hepatitis B, hepatitis C (on indication)) should be checked to prevent reactivation. The usefulness of serologic testing for Epstein-Barr Virus (EBV) before the initiation of any thiopurine, and subsequently avoiding them in EBV IgG negative IBD patients, is still debated. Thiopurine use has been associated with potentially fatal and severe EBV primary infections and post infectious lymphoproliferative disorders although the incidence seems to be low [38]. The CESAME (Cancers et Sur-risque Associé aux Maladies Inflammatoires Intestinales en France) study found an incidence of post-mononucleosis lymphomas of 0.1 per 1000 patients years rising up to 3 per 1000 patients years in young, seronegative males. Although a study performed in a pediatric population found that 4 of the 5 patients who developed hemophagocytic lymphohistiocytosis (HLH) had a primary EBV infection and were treated with a thiopurine, this still represented an incidence rate of 0.2 per 1000 patients years [38, 39]. Moreover, in the United States more than 89% of adults are seropositive for EBV and, according to a retrospective analysis, approximately 45% of seronegative IBD patients who underwent a screening before initiation of therapy still received thiopurine [40, 41]. Given this high exposure to EBV in adulthood and the low incidence of HLH and post-mononucleosis infections there are articles who doubt the usefulness and cost-effectiveness of serologic testing for EBV before thiopurine initiation [41-43]. This uncertainty about the usefulness of EBV screening also emerged in our hospital, consequently leading to an ambiguous policy.

After prescribing a thiopurine safety monitoring must be performed on regular basis in all patients. We recommend to measure liver tests (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and gamma-glutamyltransferase), C-reactive protein and complete blood count including white blood cell count (WBC) at baseline and after 1, 2, 4, 8 and 12 weeks and after that every 3-4 months during maintenance therapy, routinely performing a liver biopsy is no longer standard of care in our center (Fig. 2). Transient elastography (FibroScan) plays no role in the safety monitoring of thiopurines [44, 45]. When there is a twofold rise of at least one liver test and if this rise is possibly related to TG use the drug must be discontinued and a rechallenge may be discussed after normalization of liver tests.

Although leukopenia is quite uncommon in TG users, when it does occur and there is a leukocyte counts between 1.0 and 3.5 x 10^9/l the TG dose should be reduced, and administration has to be stopped when the leukocyte count is lower than 1.0 x 10^9/l. We recommend performing an abdominal ultrasound followed by a liver biopsy in patients with persisting liver test abnormalities (especially an elevated alkaline phosphatase level) and/or a persisting low platelet count (<150 x 10^9/l) since these are associated with (non-cirrhotic) portal hypertension and NRH (Fig. 2).

THERAPEUTIC DRUG MONITORING

During conventional thiopurine therapy, TDM can be used to explore why patients are intolerant or resistant to therapy, for dose adjustment but also to predict dose-dependent adverse events such as hepatotoxicity (due to elevated 6-MMP levels) or myelotoxicity [46]. Myelotoxicity is mostly ascribed to high concentrations of 6-TGN; however, extremely high 6-MMP concentrations are also associated with myelotoxicity, assumingly by the inhibition of *de novo* purine synthesis [7, 8]. In clinical practice we aim at 6-TGN levels between 300 and 600 pmol/ 8 x 10^8/l RBC, measured with the method of Dervieux since this range is associated with a higher chance of effectiveness [47]. It is important for clinicians to be aware of the kind of method, Lennard or Dervieux, which is used to determine the metabolites, since the erythrocyte 6-TGN concentration is higher in the Dervieux method compared to the Lennard method [48].

In contrast to conventional thiopurines, data on the utility of TDM during TG treatment are sparse and the correlation between measured 6-TGN concentration and effectiveness of TG therapy is not yet elucidated [47, 49-51]. A recent study concluded that 6-TGN levels were higher in the clinical responders and suggested a rounded cut-off value for effectiveness of therapy ≥700 pmol/ 8 x 10^8/l RBC (measured according to Dervieux method). However, more research is mandatory before this cut-off value may be considered in clinical practice [27]. It must be emphasized that TG is converted into relatively high 6-TGN levels without inducing myelotoxicity, which would be the case with high levels of 6-TGN during AZA/MP therapy [52].

Myelotoxicity during treatment with low-dose TG is rare and when it is encountered, it is often transient and most patients do not require cessation of therapy [21, 37].

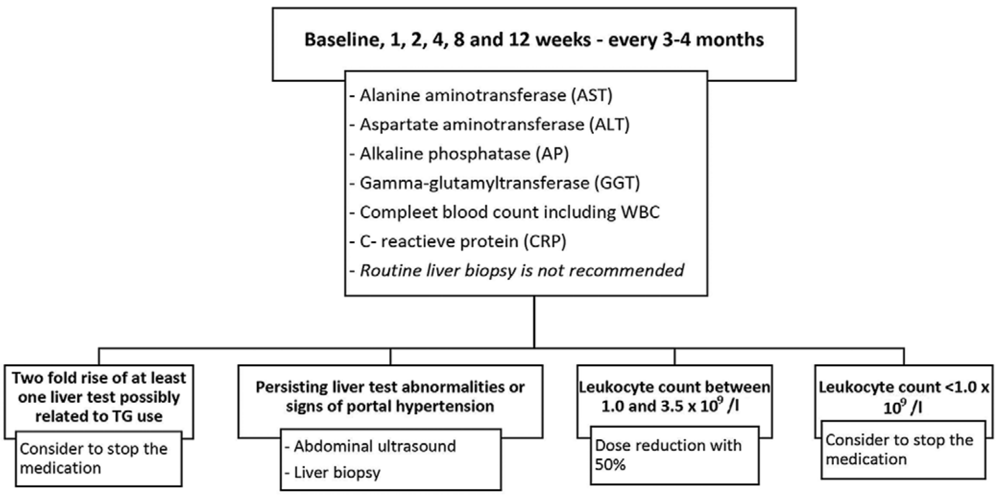

Fig. 2. Flowchart of controls in thioguanine therapy and how to act in case of abnormalities.

Interestingly, in a retrospective study (n= 266) a positive correlation between 6-TGN concentration and WBC or platelet count was demonstrated, in contrast to the negative correlation between 6-TGN and WBC in AZA or MP users [53]. This may implicate that the effect of TG on bone marrow function is limited and underlines the clinical observation that leukocytopenia is quite uncommon in TG users. This may suggest that TG might also be indicated for AZA/MP induced leukopenia as an escape drug. Nevertheless, there are also two cases in the literature describing severe pancytopenia during TG treatment due to extremely elevated 6-TGN levels caused by TPMT deficiency [54, 55].

Also during conventional thiopurine therapy, diminished TPMT enzyme activity could lead to severe myelotoxicity which can be prevented by initiating thiopurine therapy in a lower dosage [56]. However, solely 25% of the occurred leukopenia during AZA or MP therapy can be ascribed to a TPMT deficiency which still leads to an ongoing debate regarding the application of preemptive TPMT genotyping before initiating therapy [57]. Even though, a recent study concluded that, in conventional thiopurine therapy, this personalized strategy of preemptive TPMT genotyping before initiating thiopurines seems to be a cost-neutral and safe option [58]. Considering the metabolism of TG, it seems likely that diminished TPMT activity is less frequently associated with myelotoxicity during TG therapy but, besides two case reports, less is known about the gene-drug-interaction between TG and TPMT in IBD. More studies need to be performed to elucidate the optimal approach with regard to preemptive TPMT genotyping, TDM and blood checks during TG treatment.

In our center we do not measure TPMT status before initiating low dose TG therapy, which is in line with the clinical European Crohn's and Colitis Organisation (ECCO) guidelines, although other hospitals perform preemptive TMPT genotyping before starting with TG to prevent severe myelotoxicity as observed in case-reports [54, 55]. Therapeutic drug monitoring is also not performed routinely in clinical practice in our center and we primarily measure metabolites in patients with a non-response to TG to rule out non-compliance. We perform frequent blood checks, which also include hematological parameters, to check for myelotoxicity.

PREGNANCY

Conventional thiopurine exposure throughout conception and pregnancy is considered to be safe [59-61]. Since 6-TGNs are the end metabolites of TG and AZA/MP, one may assume that these three drugs have the same effect on pregnancy outcome. There is a lack of sufficient data regarding the safety during pregnancy and teratogenicity of TG. There is a small study which shows reassuring outcomes and suggests safe use of TG during pregnancy, but all these seemingly encouraging data are based on a limited number of patients (13 patients, 19 pregnancies) [62]. Further short- and long-term cohort studies are required to confirm the safety in pregnant women. In our center we discuss each patient in a case by case manner, and after a thorough consultation by the gynecologist, if the continuation of TG during pregnancy to maintain remission and prevent a flare-up is advisable.

NODULAR REGENERATIVE HYPERPLASIA

One of the feared complications during TG therapy is the occurrence of sinusoidal obstruction syndrome and especially NRH which is not always reflected in changes of liver function tests [33, 63, 64]. However, in contrast to earlier observations, the development of TG induced NRH appears to be dose-related. A recent systematic review which included 42 articles about the hepatotoxicity of 6-TG showed that NRH occurs in 14% of patients treated with a daily dose of approximately 0.6 mg/kg and rarely occurs at low cumulative doses (i.e. 0.2-0.3 mg/kg) [29]. Secondly, NRH is not specifically correlated with TG, but is also common with conventional thiopurines and IBD itself [29, 33, 65-67]. Furthermore, it had been observed that NRH rarely led to symptoms of portal hypertension or liver transplant and was clinically insignificant in most patients [68, 69]. These findings were supported by a recent study which demonstrated that vascular liver abnormalities of any degree were commonly observed in long-term TG treated IBD patients, but these were rarely progressive and of limited clinical relevance [70].

There are indications that NRH is potential reversible, demonstrated by a normalization of alkaline phosphatase and platelet count, a reduction in the hepatic venous pressure gradient after discontinuation of TG therapy and symptoms of non-cirrhotic portal hypertension also appeared to resolve in one-third [71, 72]. Longer follow up data after discontinuation of such patients are needed.

Due to these new insights we do not routinely perform ultrasonography or liver biopsies in our patients with TG anymore but conduct these only in case of a high level of suspicion: after an abnormal abdominal ultrasound, in symptomatic patients with symptoms of portal hypertension (e.g. platelet count <150 x 10^9/l, varices, ascites, hepatic encephalopathy) or persisting liver test abnormalities (especially an elevated alkaline phosphatase level) without another plausible explanation. The FibroScan has little added value in the safety monitoring of thiopurines since there is no fibrosis in patients with NRH. Moreover, the study by Laharie et al. [44] demonstrated that the results of the FibroScan do not correlate with the portal or perisinusoidal fibrosis on biopsy and there also seems to be no correlation between liver stiffness and portal hypertension. These findings were confirmed by Meijer et al. [45] who also did not find a significant difference in liver stiffness between patients treated with thiopurines with biopsy confirmed abnormalities and patients without.

CANCER RISK

The use of AZA/MP is associated with a higher risk of the development of lymphoproliferative disorders, but this increased risk diminished after discontinuation of therapy [73]. Furthermore, there is an increased risk of the development of non-melanoma skin cancer according to a meta-analysis (8 studies, n=60,351) involving IBD patients using AZA/MP [74]. Mutagenic properties have been described to TG as well and the reported increased risk of cancer during therapy with AZA/MP may also apply to TG [75]. One cohort study, including 274 TG-using IBD patients (median dose 20 mg/d) with 1567 patient-years of follow-up, showed that 9 patients (3.3%) developed moderate malignancies (i.e. 5 non-melanoma skin cancers, 2 melanoma skin cancers and 2 solid organ cancers). Two patients (0.7%) developed severe graded malignancies (i.e. 1 non-Hodgkin lymphoma and 1 Merkel cell carcinoma) leading to a discontinuation of TG [27]. Patients need to be informed about the probable increased risk of malignancy before therapy is initiated and the importance of daily sun protective measures and 'self-skin exams', especially in countries with a high number of sunshine hours since the risk for non-melanoma skin cancer is related to cumulative sunlight exposure [76].

FUTURE PERSPECTIVES

Recent discoveries have provided additional information about the metabolism of TG. In contrast to AZA/MP, the gut microbiome is able to convert TG to the therapeutically effective 6-TGN [77]. These findings were confirmed in Winnie mice which experienced a rapid improvement of the colitis in regions of the colon with direct contact to rectally administrated TG; this was in contrast to mice treated with topical MP [78]. These data suggests that local delivery of TG could lead to a conversion of TG to 6-TGN by the microbiome without the requirement of host metabolism, leading to an additional mode of action of local immunosuppression. Following these findings controlled-release oral formulations of TG are being developed and even a few patients were treated with daily TG enemas or suppositories with a rapid treatment response and with low systemic bioavailability of 6-TGN [79]. Although future studies are needed to confirm these findings, they pave the way for therapy with TG enemas or oral delayed-release preparations which, in contrast to the current situation, will permit a more rapid therapeutic action of TG with potential avoidance of unwanted systemic adverse effects.

CONCLUSIONS

Thioguanine is formally registered for IBD patients in the Netherlands who previously failed conventional thiopurine therapy due to lack of response or adverse effects. The TG toxicity profile is relatively mild and the reported incidence of NRH related to TG use seems comparable to conventional thiopurines and the background incidence of NRH in IBD patients. Routine monitoring of laboratory parameters and adverse events is recommended, comparable to the monitoring of patients on conventional thiopurine therapy.

Conflicts of interest: N.K.B. has served as a speaker for AbbVie and MSD and has served as consultant and principal investigator for TEVA Pharma BV and Takeda. He has received a (unrestricted) research grant from Dr. Falk, TEVA Pharma BV, MLDS and Takeda. The other authors declare no conflicts of interest.

Authors' contributions: F.C. conceived the study. F.C. drafted the first version of the manuscript. M.S., C.J.J.M., N.K.B. and H.J.C.B. critically revised the manuscript. All authors approved the final version to be published and agree to be accountable for all aspects of the work.

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