PART IV

APPENDICES
APPENDIX I

DOSING TIOGUANINE 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 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 tioguanine 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 tioguanine therapy and discuss the reported hepatotoxicity of tioguanine (especially nodular regenerative hyperplasia). We propose expert-based guidelines for balanced treatment.
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 drugs of choice for steroid-dependent and steroid-refractory disease and for maintenance therapy, 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\(^1\). Methotrexate (MTX) is also effective for this maintenance indication, at least in patients in whom remission has been achieved by this immunosuppressive agent\(^2\). Regular infusions of infliximab (IFX) or adalimumab (ADA) subcutaneous may be considered as maintenance option in CD patients who are refractory or intolerant to conventional thiopurines or MTX. However, in 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 tioguanine (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 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 TG.

Rationale for tioguanine therapy

Most of the clinical and pharmacological data on TG stems from studies in haematological malignancies. In IBD, treatment with 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, TG has been considered as an alternative treatment option in IBD patients who failed therapy with the conventional thiopurines due to intolerance or refractoriness. Theoretically, TG has several potential metabolic advantages when compared to AZA and 6-MP. The first metabolic difference of TG is its direct conversion into the pharmacologically active tioguanine nucleotides (TGN) (Figure 1). As compared to the metabolism 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 TGN which may lead to myelotoxicity. It is believed that TPMT has a less central role in the metabolisation of TG, hence induction of hepatotoxicity and myelotoxicity may be limited.

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 TG metabolism.

In conclusion, the apparent metabolic advantages of TG compared to the conventional thiopurines are the more direct conversion into 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 tioguanine

Initial short-term reports on the toxicity profile of TG were comforting. 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 TG. The authors concluded that this serious complication was idiosyncratic and that 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 TG administered in this study was not reported accurately, whilst the observed median TGN level was approximately 1250 pmol/8x10^8 RBC. As response, several other research groups published their data on TG therapy and the prevalence of NRH (Table 1). These subsequent studies appear to show a dose-dependent NRH effect with no or only few cases of NRH (0-4%) observed in the patient groups treated with a maximum daily dose of 24mg TG. In patients treated with reported higher dosages (40 to 80mg per day), NRH was observed in 0 to 27% of liver biopsies. 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). 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 TG effect.

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

Proposed expert-based guidelines on safety monitoring

In 2004, an European TG working party formulated the following expert-based guidelines for future TG administration: TG may be considered in IBD patients with 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 TG. However, only 30-40 % of the UC patients treated with biologics therapy were in remission after 12 months.

Based on the recent published data, we recommended the following practices. We obtain written informed consent from the patient after providing adequate information on its (hepato-)toxic profile, especially as IBD is an off-label indication of TG. It is recommended that TG administration should be started at a dosage of approximately 20 mg per day and should not exceed 25mg daily. Safety monitoring is of pivotal significance during TG therapy and must be performed on a regular basis in all patients. The drug has to be withdrawn in case of a twofold rise of at least one liver test if at least possibly related to TG use. The TG dose should be reduced when leukocyte counts are ≥ 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 liver specimen after one, three and, then after every three years of TG treatment. Staining with haematoxylin and eosin (H&E), (silver)reticuline and trichrome are mandatory\textsuperscript{16}. If histological abnormalities consistent with NRH are found in the specimens the treatment of TG should be discontinued. Therapeutic drug monitoring (measuring TGN levels in erythrocytes) is of limited value during TG therapy, however might help to interpret the occurrence of some adverse events. To determine the patients compliance measurement of TGN remains the gold standard. Contradictory results have been published in case reports about the potential teratogenic effects of TG in leukaemia patients. There is one case report on the use of TG in an IBD patient during pregnancy and demonstrated no teratogenic effects\textsuperscript{17-19}. Further studies are needed to determine how safe the use of TG is during pregnancy or lactation in IBD patients. For that reason, TG should be avoided during pregnancy or lactation.

### Dosing of tioguanine

Formal dose-ranging studies are lacking and only limited data are available on therapeutic efficacy and dosing regimens. 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 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\textsuperscript{20}.

### CONCLUSION

tioguanine remains to 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 TG use is of general concern but may well be comparable with conventional thiopurines use. Moreover, IBD itself should probably be considered as a risk factor to develop NRH. Nevertheless, monitoring remains advocated.

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**Table 2. Drug monitoring of TG.**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>At which moment?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete blood count</td>
<td>Baseline, 1, 2, 4, 8 and 12 weeks. Every 3 months</td>
</tr>
<tr>
<td>Tioguanine nucleotides</td>
<td>Optional to check patient compliance</td>
</tr>
<tr>
<td>Alanine aminotransferase</td>
<td>Baseline, 1, 2, 4, 8 and 12 weeks. Every 3 months</td>
</tr>
<tr>
<td>Aspartate aminotransferase</td>
<td>Baseline, 1, 2, 4, 8 and 12 weeks. Every 3 months</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>Baseline, 1, 2, 4, 8 and 12 weeks. Every 3 months</td>
</tr>
<tr>
<td>Gamma-glutamyl transferase</td>
<td>Baseline, 1, 2, 4, 8 and 12 weeks. Every 3 months</td>
</tr>
<tr>
<td>Bilirubine</td>
<td>Baseline, 1, 2, 4, 8 and 12 weeks. Every 3 months</td>
</tr>
<tr>
<td>C-reactive protein (efficacy control)</td>
<td>Baseline, 1, 2, 4, 8 and 12 weeks. Every 3 months</td>
</tr>
</tbody>
</table>
**REFERENCE LIST**


8. van Asseldonk DP. Liver histology of IBD patients who are treated with tioguanine due to failure of conventional thiopurines reveals very few cases of nodular regenerative hyperplasia [abstract]. Gastroenterology. 2010.

9. van Asseldonk DP. Liver histology of IBD patients who are treated with tioguanine due to failure of conventional thiopurines reveals very few cases of nodular regenerative hyperplasia [abstract]. Gastroenterology. 2010.


