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# Is thioguanine-associated sinusoidal obstruction syndrome avoidable? Lessons learned from 6-thioguanine treatment of inflammatory bowel disease and a mouse model

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### SUMMARY

6-thioguanine (6TG) has become the 'ugly sister' of azathioprine and 6-mercaptopurine since it has been associated with sinusoidal obstruction syndrome (SOS) of the liver. Although the overall toxicity profile of 6TG seems superior to that of the other thiopurines, further use of 6TG was largely discarded due to fear of this complication and related hepatic nodular regenerative hyperplasia and veno-occlusive disease. There is emerging evidence showing that 6TG-associated SOS is a dose-dependent and reversible phenomenon. Therefore, it is urged that the use of 6TG in inflammatory bowel disease be reconsidered; randomized controlled studies are warranted.

**Keywords:** 6-thioguanine; sinusoidal obstruction syndrome; veno-occlusive disease; nodular regenerative hyperplasia; leukemia; inflammatory bowel disease.

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# RESUMO

A tioguanina está associada à síndrome da obstrução sinusoidal evitável? Lições aprendidas com a 6-tioguanina no tratamento da doença inflamatória intestinal em modelo de ratos

A 6-tioguanina (6TG) tornou-se "a irmã feia" da azatioprina e da 6-mercaptopurina, pois tem sido associada à "síndrome da obstrução sinusoidal" (SOS) do fígado. Embora o perfil de toxicidade geral da 6TG talvez seja superior ao de outras tiopurinas, a continuação do uso de 6TG foi amplamente descartada devido ao medo dessa complicação e das relacionadas à hiperplasia hepática nodular regenerativa e doença veno-oclusiva. Evidências emergentes demonstram que a SOS associada à 6TG é um fenômeno dose-dependente que pode ser revertido. Portanto, é urgente que o uso do 6TG na doença inflamatória intestinal seja reconsiderado; são necessários estudos randomizados e controlados.

**Unitermos:** 6-tioguanina; síndrome da obstrução sinusoidal; doença oclusiva venosa; hiperplasia nodular regenerativa; leucemia; doença inflamatória intestinal.

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#### INTRODUCTION

6-thioguanine (6TG) is the ugly sister of the thiopurines, azathioprine (AZA) and 6-mercaptopurine (6MP), because of its strong association with sinusoidal obstruction syndrome (SOS) of the liver, previously named and overlapping with veno-occlusive disease (VOD) and nodular regenerative hyperplasia (NRH). The first cases of SOS attributed to 6TG were reported in 19821,2, although the possibility had been raised earlier in the literature<sup>3</sup>. Those of us who embarked on 6TG treatment for inflammatory bowel disease (IBD) in the beginning of the 21st century either did not know of this literature or had forgotten it. However, shortly after the initial enthusiasm for 6TG in IBD, the gastroenterological world was reminded of SOS by Dubinsky et al.4, in what has become an influential study. These investigators concluded that SOS was idiosyncratic, rather than doserelated, and that it was therefore unsafe to use 6TG at any dose. The manuscript has many problems including not least that the dose of 6TG in its patients was never well characterized, but notwithstanding most other groups have been wary of using 6TG since the publication of this paper and especially given that there is no reliable test for SOS.

There is also a widely held concern that SOS is irreversible, although interestingly one of the earliest detailed reports of 6TG-induced SOS concluded on the basis of sequential liver histology that SOS was to a large degree reversible<sup>2</sup>. More recently, a concern has been raised that SOS may be a thiopurine class effect<sup>5</sup>, although the rate of SOS with AZA or 6MP does not seem to be different from that in the background population.

# SINUSOIDAL OBSTRUCTION SYNDROME

Ongoing sinusoidal obstruction syndrome (SOS) manifests in time with various degrees of tender hepatomegaly, ascites, hyperbilirubinemia, persistent thrombocytopenia, and increased portal venous pressure, which in turn may give rise to splenomegaly, esophageal varices and their complications. While the pathogenesis is not completely understood, sinusoidal endothelial injury resulting in the loss of sinusoidal wall integrity is believed to play a significant role. Intrasinusoidal cytotoxic CD8+ T lymphocytes seem to be involved<sup>6</sup>. Histopathological findings include sinusoidal dilatation with accumulation of erythrocytes in both the sinusoids and the perisinusoidal spaces (space of Disse). Specific morphological abnormalities such as peliosis hepatis and nodular regenerative hyperplasia (NRH) frequently accompany SOS, likely reflecting a common pathogenesis<sup>7</sup>.

# 6-THIOGUANINE, SINUSOIDAL OBSTRUCTION SYNDROME AND IBD

In 1966, more than ten years after its discovery, 6TG was first used in the treatment of IBD. Its therapeutic efficacy seemed promising, albeit nausea, sensory loss with unsteadiness of gait or liver test abnormalities necessitated therapy withdrawal in these patients8. 6TG was then not used in IBD treatment until its reintroduction around 2001, when Dubinsky et al. reported on its successful use in Crohn's disease patients who had failed conventional thiopurine therapy9. Following their promising results, other researchers began to use 6TG in IBD treatment, mostly with success. Although a controlled clinical trial was never performed, available studies showed 6TG efficacy (Table 1) and tolerability (Table 2) to be favorable. In 2003, however, the use of 6TG in IBD patients was linked with NRH; and as a consequence further use was discouraged4. Other researchers appeared to corroborate the association between the use of 6TG in IBD and the occurrence of NRH/ VOD/ SOS.

Seiderer et al.<sup>10</sup> reported NRH in 16 out of 45 liver biopsies from a selected group of IBD patients using 6TG after failing conventional thiopurine treatments.

**Table 1** – Efficacy of thioguanine in IBD treatment

Author	n	IBD	Daily dose (mg)	Duration (months)	Response* (%)	Reference (nr)
Dubinsky et al. <sup>9</sup>	10	CD	40	4	70%	(9)
Cheung et al. <sup>24</sup>	15	CD+UC	80	3	73%	(24)
Dubinsky et al. <sup>25</sup>	21	CD+UC	20-40	9	88%	(25)
Herrlinger et al. <sup>26</sup>	39	CD	40-80	6	87%	(26)
Herrlinger et al. <sup>27</sup>	16	CD	20-40	12	83%	(27)
Bonaz et al. <sup>28</sup>	49	CD	20	12	79%	(28)
Teml et al. <sup>29</sup>	20	UC+IC	40	6	69%	(29)
Qasim et al. <sup>30</sup>	40	CD+UC	40	6	72%	(30)
Ansari et al. <sup>31</sup>	30	CD	40	6	60%	(31)

IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; IC, indeterminate colitis. \*Response rates were assessed according to criteria used by the separate authors.

**Table 2** – Tolerability of thioguanine in IBD treatment

Author	n	IBD	Daily dose (mg)	Duration (months)	Tolerability* (%)	Ref.
Herrlinger et al. <sup>26</sup>	37	CD	20-40	6	84%	(26)
Dubinsky et al. <sup>25</sup>	21	CD+UC	20-40	9	81%	(25)
Derijks et al. <sup>32</sup>	32	CD+UC	20-40	2	81%	(32)
Bonaz et al. <sup>28</sup>	49	CD	20	12	90%	(28)
De Boer et al. <sup>33</sup>	95	CD+UC	20-40	12	79%	(33)
Teml et al. <sup>34</sup>	296	CD+UC+IC	20-40	12	76%	(34)
Qasim et al. <sup>30</sup>	40	CD+UC	40	9	67%	(30)
Almer et al. <sup>35</sup>	23	CD	20-60	> 12	57%	(35)
Van Asseldonk et al. <sup>36</sup>	46	UC	20	> 12	87%	(36)

IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; IC, indeterminate colitis. \*Tolerability rates were assessed according to criteria used by the separate authors.

However, these authors did not provide causes for failure with first-line thiopurine therapies, or described whether laboratory abnormalities indicative of liver pathology were present prior to 6TG initiation. On the other hand, Dutch authors postulated a dose-dependent effect, supported by studies in which a lower frequency of NRH was observed when using a lower dosage of 6TG<sup>11,12</sup>. This dose-dependent effect was confirmed in a large prospective Dutch cohort of 99 IBD patients using 6TG at a daily dose of approximately 20 mg, about half the dose used in previous studies. All patients underwent liver biopsies, but only four cases (4%) of NRH were identified after a median treatment duration of over two years<sup>13</sup>. This prevalence appears not different from that of control populations<sup>14,15</sup>. Table 3 summarizes the NRH/SOS

frequencies observed in different studies and illustrates that its occurrence during 6TG therapy is likely to be dose-dependent. Furthermore, 6TG-associated NRH appeared to be reversible as illustrated by a reduction in portal venous pressure after cessation of 6TG therapy<sup>16</sup>. In conclusion, the use of 6TG in IBD is defensible with close clinical monitoring, and likely to be preferable to conventional thiopurines in many patients provided that daily doses are low.

### PHARMACOLOGICAL CONSIDERATIONS

If 6MP and 6TG are equally dosed, erythrocyte thioguanine nucleotide (6TGN) concentrations are about tenfold higher with 6TG than with MP<sup>17</sup>. This is believed to be due to the more direct conversion of 6TG into 6TGN

Table 3 - Observed frequencies of NRH in IBD patients using TG

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Author	n	TG dose (mg)	TGN* (pmol/8x10*8 RBC)	Biopsies (n)	NRH (n, %)	Ref
Geller et al. <sup>37</sup>	111	40 (20-80)	1230 (530-2310)	38	20/38, 53%	(37)
Gilissen et al. <sup>38</sup>	13	19 (6-20)	705 (SD 332)	13	0/13, 0%	(38)
Teml et al. <sup>34</sup>	296	20-40	-	60	16/60, 27%	(34)
Ferlitsch et al. 16	26	40 (20-80)	-	24	6/24, 25%	(16)
De Boer et al. <sup>39</sup>	28	20 (5-40)	564 (SD 278)	28	2/26, 8%	(39)
Ansari et al. <sup>31</sup>	30	40 (20-60)	807 (105-2545)	11	0/11, 0%	(31)
Almer et al. <sup>35</sup>	23	40 (20-60)	600 (99-2488)	2	0/2, 0%	(35)
Van Asseldonk et al. <sup>36</sup>	99	20 (10-24)	463 (SD 270)	99	4/99, 4%	(13)

NRH, nodular regenerative hyperplasia; IBD, inflammatory bowel disease; TG, thioguanine; TGN, thioguanine nucleotides; \*TGN are expressed as medians with their range or mean with standard deviation (SD).

compared with 6MP and the fact that erythrocytes are deficient in the rate-limiting inosine monophosphate dehydrogenase enzyme responsible for the conversion of 6MP into 6TGN<sup>18</sup>. These differences are nicely illustrated by Lancaster et al.<sup>19</sup>, who showed that if 75 mg of 6MP per square meter of body surface was compared to 43 mg of 6TG per square meter of body surface, then RBC 6TGN concentrations were around six times higher with 6TG, whereas 6TGN concentrations in leukocytes, the actual target cells, were comparable.

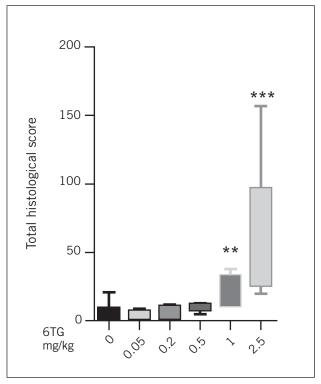
A high erythrocyte 6TGN concentration may be a risk factor for SOS because contrasting results on the role of thiopurine S-methyltransferase (TPMT) activity in 6TG-associated SOS have emerged<sup>20,21</sup>, which suggest that higher TPMT and, therefore, lower 6TGN is less damaging. In the treatment of leukemia, methotrexate (MTX) is often used alongside 6MP and 6TG. A synergistic effect between MTX and 6MP has been shown in vitro and in vivo, and it is believed to be associated to the inhibitory effect of MTX on purine de novo synthesis<sup>22</sup>. A similar synergistic effect between MTX and 6TG has been hypothesized, but not proven. It may be that such a synergism not only increases the therapeutic efficacy but also aggravates SOS, which in turn might be diminished with 6TG monotherapy or a lower 6TG dose or higher TPMT activity.

## A NOVEL ANIMAL MODEL OF 6TG

To explore whether 6TG SOS/VOD is idiosyncratic, or 6TG dose-related, or a class effect of thiopurines, we have evaluated in Brisbane, Australia, a novel acute mouse model. To date no animal model of 6TG or thiopurine related VOD has been published. In particular, VOD was screened for, but not detected by Hartford et al. in C57BL6 mice<sup>23</sup>. This report is a brief one because a full report is being prepared. C57BL6 mice were gavaged with different amounts of 6TG, 6MP, or the methylated metabolites of these purine bases. SOS was assessed by a blinded observer using a total damage score made up of endothelial, hepatocyte and inflammatory cell subscores. Peripheral blood was analyzed. Only 6TG resulted in histology damage consistent with SOS. This was apparent as early as three days depending on dose, but was consistently seen at 9-14 days when gavaging 6TG 2.5 mg/kg/d.

The major finding was sinusoidal dilatation, as well as congestion and damage and loss of central vein endothelial cells, which was apparent at ultrastructural level and with staining of endothelium with Von Willebrand Factor. There were also subtle liver parenchymal changes apparent on conventional hematoxylin and eosin staining, and a marked inflammatory cell infiltrate was readily apparent with F4/80 staining for macrophages. The effect was very dose-dependent with a dose threshold

for the histological findings above 0.5 mg/kg/d 6TG at 14 days. This threshold was lower at 14 days than three days, but the threshold did not decrease over a longer period of once daily gavage for 28 days, suggesting that the effect was not cumulative over this time period. The white cell count was reduced in a dose-response manner with white cells being 50% of control at 14 days with 0.5 mg/kg 6TG once daily gavage (Figure 1). A significant further reduction in white cell count was not recorded with daily gavage of 0.5 mg/kg 6TG to 28 days.



**Figure 1** – Histological changes with 6TG gavage therapy over 14 days are dose-dependent.

# FINAL CONSIDERATIONS

The Dutch experience with a large clinical trial and associated liver biopsy data concerning 6TG treatment of IBD are very reassuring, but remain uncontrolled. The results of the novel mouse model for 6TG-induced SOS are consistent with the Dutch clinical experience. Taken together, it is concluded that 6TG therapy at low doses is not associated with significant SOS/NRH. Therefore, given that there are adverse drug reactions experienced by many patients prescribed conventional thiopurines, azathioprine or 6-mercaptopurine, we believe that there is good reason to conduct a properly powered and controlled prospective clinical trial to compare the clinical efficacy and safety of low dose 6TG versus conventional thiopurines.

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