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# Hepatobiliary Manifestations Induced by Thiopurines during IBD

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**ABSTRACT**

Thiopurines(TP) are frequently used in inflammatory bowel disease, especially in remission maintenance. One of the reasons for stopping these treatments is appearance of side effects. In this study, we focus on liver damage induced by thiopurines by specifying their types, their mechanisms, and practical behavior in order to diagnose them early and avoid their aggravation This is a retrospective and descriptive study on monocentric cohort of 115 patients followed for IBD under TP recorded over a period from January 2009 to January 2019. 11 patients had disorder of liver function test, a prevalence of 9.5%, which occurred in half of patients, three months from the start of treatment. 3 (2.6%) patients had abnormal liver test and 8 (7%) had hepatotoxicity. occurrence of hepatotoxicity has resulted in stopping treatment in 4 (36.3%) patients. There was no difference in toxicity between azathioprine and 6-mercaptopurine (p=0,081). The incidence of hepatotoxicity in patients with inflammatory bowel disease receiving thiopurines is not negligible. In our clinical practice, it is advisable to start the treatment gradually, to carry out a well codified clinical and biological control, and to pay particular attention to drug interactions.



## Introduction

Thiopurines TP are recommended in management for Crohn's disease (CD) and ulcerative colitis (UC), they include azathioprine (AZA), 6-mercaptopurine (6-MP) and 6-thioguanine most used in hematology. They have potent antiproliferative and immunosuppressive activity and are indicated in remission maintenance. It is estimated that about two thirds of patients with CD will have TP treatment during their follow-up. (1)

Effectiveness of these molecules varies widely according to studies, a variability partly explained by discontinuation of treatment following adverse effects.

Among these undesirable effects, liver toxicity which can manifested by a disturbance of liver function tests (cytolysis / cholestasis) or by vascular lesions such as nodular regenerative hyperplasia (NRH).

The aim of our study is determine the prevalence and profile of liver toxicity in IBD patients under TP.

## Materials and method

This is a retrospective and descriptive study of monocentric cohort of 582 IBDs, 115 of which were under TP recorded over a period from January 2009 to January 2019 in the hepato-gastroenterology department.

These patients were followed in IBD consultation on a regular basis, and benefited from monitoring by (CBC + liver hepatic function 1/week during the 1st month then once/ month during 3 months then every 3 months.

We included all patients on thiopurine at the dose of (AZA 2–2.5 mg/kg/day or 6MP 1–1.5 mg/kg/day) with disturbance liver function tests:

-Abnormal liver function was defined by an increase between 1 and 2 times normal in the value of one or more liver enzymes (AST, ALT, GGT, ALP, BT),

-Hepatotoxicity was defined by increase more than twice the normal of the above enzymes.

Excluded were all patients with history of liver disease, patients who received TP for other indications, as well as all those who were taking other concomitant therapy with thiopurines.

At the time of liver test disturbance detection, an etiological assessment was carried out comprising first of all: interrogation looking for other concomitant medication taken, alcoholism, recent serology, assessment of autoimmunity, hepatic MRI and in second-line liver biopsy.

We used SPSS20 software for the statistical study (the significance threshold was set at 0.05)

## Result

115(20.1%) patients were on TP followed for MICI. AZA was prescribed in 72 (62.6%), patients 6-MP was prescribed in 43 (37.4%) patients .102 (89%) patients had CD and 13 (11%) had UC.

40 patients presented undesirable effects to thiopurines either a prevalence of 35%, which 11 (9.5%) patients had liver function test disorder. The mean age of these patients was 36.38 +/- 9.3 years, with a female predominance of 63.6% (n = 7) sex ration F / M 1.7. Among them 5 (45.45%) were on AZA and 6 (54.54%) on 6-MP. During the occurrence of the side effect, the dosage was on average for AZA, 2.15 +/- 0.25 mg / kg / day and for 6- MP 1,5 +/- 0,37 mg / kg /day. Liver function test disorder was found beyond 3 months of treatment start in more than half of the cases (54.5%). Among these 11 patients, 3 (27.27%) had abnormal liver test which did not exceed twice the normal and had normalized on the consecutive controls without adjustment of treatment. The 8 (72.72%) other patients had hepatic test greater than 2 * ULN having imposed a reduction of thiopurines doses by half with close monitoring every week, among them (4 (50%) had cytolytic hepatitis, three (37.5%) had mixed hepatitis and one (12.5%) patient had isolated anicteric cholestasis). Clinically, fatigue was noted in 5

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(62.5%) patients and jaundice in one (12.5%) patient. A return to normal liver function tests was noted in half (50%) of the patients in whom (one (25%) had isolated cholestasis another patient (25%) had mixed hepatitis and two (50%) had cytolytic hepatitis). The normalization median was 41.3 ± 25 days, while in remaining half, the liver enzymes continued to increase, thus stopping treatment. The diagnosis of drug-induced hepatitis was confirmed by liver biopsy in 2 patients "having presented mixed hepatitis" with metabolites assay showing 6MMP> 5700pmol /8.108GR) the median rate of 6TGN was 250.8pmol / 8.108GR) reference value (235-450pmol / 8.108GR), we still opted for a switch to another therapeutic class. Sclerosing cholangitis was diagnosed on MRI data in patient with cholestatic jaundice, and hepatitis B in the fourth patient with isolated cytolysis. These latter were not considered to have hepatotoxicity.

**Discussion**

The prevalence of hepatotoxicity induced by thiopurines varies by studies between 3 and 10% partly due to the absence of consensus definition of hepatotoxicity induced by thiopurines. Generally, the accepted definition is that proposed by "the Council for International Organizations of medical sciences" in 1990 according to which hepatotoxicity is defined by an increase in the levels of ALT or ALP greater than 2 times the upper limit of normal (ULN) (2).

More than half of hepatotoxicity in our study occurred during the first trimester of treatment, which explains the need for close monitoring at the start of treatment. In fact, in a prospective Bastida study of 161 patients treated with TP for their IBD over a median period of 271 days, abnormal liver test and hepatotoxicity were detected in 13% and 10% of the patients, respectively. In 50% of these patients, the abnormalities appeared during the first 3 months of treatment. (3).

In a systematic review of the literature, including 138 patients who received AZA / 6MP, the incidence of hepatic disturbance and hepatotoxicity was 7.1% and 2.6%, respectively. These were mainly retrospective studies (4).

No statistically significant difference was found in terms of hepatotoxicity between AZA and 6-MP (p 0,081). Indeed, in Gisbert's review, the average incidence of hepatotoxicity was 2.1% (95% CI :1.6–2.9%) and 2.7% (95% CI: 1.8–4.1%) respectively for AZA and 6-MP thus suggesting a similar risk for the two molecules and not influencing the choice of one molecule over the other (4)

Three forms of hepatotoxicity are observed: transient elevation of the hepatic tests mainly of transaminases which occurs in 5% to 15% of cases (5), and normalizes during follow-up without any dose adjustment. In our series, 4 patients had an elevation of liver tests without clinical symptoms with spontaneous resolution. A second form has been observed: idiosyncratic cholestasis, which generally occurs after 2 to 12 months of treatment (6,7), which is often associated with immunoallergic manifestations such as rash, fever, pancreatitis and arthralgia. The prevalence of this immunoallergic disorder varies between 1 and 5% (8) which would be favored by genetic factors (9). The imidazole compound of azathioprine is responsible for immunoallergic clinical manifestations and 6-MP part is believed to be cause of liver damage (10), one case was reported in the present study with AP at 3*ULN after two months of treatment. A third form of hepatotoxicity by venous-occlusion that occurs when doses are high, the latter is associated with cases of regenerative nodular hyperplasia (RNH), a rare chronic hepatic injury linked to long-term treatment with TP especially 6- TG (11,12) and which can be complicated by portal hypertension. We did not find any case of HNR

The mechanisms by which thiopurines induce hepatotoxicity have not yet been elucidated. The high level of final metabolites of AZA and 6 MP (6-MMP and 6 MMPR), found in patients with hepatotoxicity, (13,14) was initially suggested as a probable cause. However, this has not been confirmed in other studies (15,16). The high level of these metabolites is usually linked to the high activity of TPMT (17), an enzyme which is involved in the metabolism of 6MP and which is subject to genetic polymorphism. In a recent meta-analysis of 10 studies including 1,875 patients, TPMT polymorphisms were not associated with hepatotoxicity (18).

There are currently no clear recommendations for for managing liver toxicity TP inducted:

Gisbert et al proposed, after reviewing 34 studies including around 3485 patients, an approach based on the rate of ALT and /or AST and /or AP and /or GGT (4):

Faced with a slight abnormality in the hepatic balance (ALT and / or AST and / or AP and / or GGT <5 ULN): they proposed to continue treatment at the same dose with closer biological monitoring (every week every months) (Grade B recommendation)

Faced with so-called severe hepatic abnormalities (ALT and/or AST and/or AP and/or GGT>5 ULN) without jaundice: they proposed to reduce the dose of AZA or 6-MP by half (50%) and to continue monitoring the biological balance at a more accelerated rate (weekly to monthly) (Grade B recommendation). Indeed, according to Dubinsky et al, reducing the dose of 6-MP allows normalization of transaminases in 100% of patients who have had hepatotoxicity induced by 6-MP (19). In the absence of normalization of liver function tests, a discontinuation of treatment is recommended (Grade B recommendation).

If the patient is taking AZA, it is possible to switch to 6-MP. In a retrospective study, Bermejo et al introduced 6-MP in 31 patients, in whom AZA was stopped for hepatotoxicity. Over a median follow-up period of 32 months, no evidence of hepatotoxicity was noted in 87.1% of the patients. Otherwise, 12.9% of patients developed signs of hepatotoxicity after 1 to 3 months from the introduction of 6-MP (20).

In a retrospective study of 179 cases with IBD on AZA or 6MP (presenting a preferential metabolism of 6MMP), administration of 6-MP was proposed twice / day instead of once / day which allowed to decrease the levels of 6-MMP (5324 against 11785 pmol / 8 × 10 ^ 8 red blood cells; p = 0.0001), while maintaining the level of 6TGN (216 against 239 pmol / 8 × 10 ^ 8) without impact on activity of inflammatory disease associated with improvement in hepatic test (21).

**Conclusion**

Liver toxicity related to thiopurines is not uncommon. It requires regular monitoring of the liver function tests.

The course of action is not consensual, however, we can propose: in the event of a slight disturbance, strict monitoring without modifying doses, and in the event of more marked anomalies, a dose reduction of half. However, in the event of significant disorders in liver function tests or persistence of disorder, treatment should be stopped.

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