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 hepat-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...
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.

References
1) Peyrin-Biroulet L, Oussalah A, Williet N et al. Impact of azathioprine and tumour necrosis factor antagonists on the