

# Liver dysfunction in patients with IBD under immunosuppressive treatment: do we need to fear?

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There is an ineluctable trend in the treatment of inflammatory bowel disease (IBD) towards an extensive use of immunosuppressive drugs. These agents are prescribed earlier in the disease,<sup>1</sup> in an increased proportion of patients (reaching one-third in some European countries<sup>2</sup>) and for prolonged periods since their impact on the disease course is unfortunately only suspensive.<sup>3</sup> As a consequence, clinicians have less to do with the well-known direct complications of IBD, but there are growing preoccupations regarding established or uncertain safety concerns related to immunosuppressive treatment. IBD specialists are living in slow motion the cultural revolution brutally experienced by HIV specialists with the arrival of efficient combined antiviral treatment: these clinicians had to turn from infectious disease specialists into experts in drug management (observance, viral resistance) and drug complications (lipodystrophy, cardiovascular problems).

Immunosuppressive drugs for IBD can be deleterious through direct toxicity on organs, and promotion of serious infections or cancers. Regarding the liver, direct toxicity of anti-tumour necrosis factor (TNF) appears anecdotal<sup>4</sup> and that of methotrexate well circumscribed and largely preventable through the experience of rheumatologists.<sup>5</sup> Direct liver toxicity of thiopurines is more problematic, representing the most frequent cause of liver injury, together with fatty liver disease, in tertiary care IBD centres.<sup>6</sup> Concordant data suggest that the prevalence and annual incidence of 6-mercaptopurine- and azathioprine-induced hepatotoxicity

are low (3% and 1.4%, respectively)<sup>7</sup>, and that dose adaptation is most cases is sufficient to resolve the problem.<sup>6, 8</sup> However, a safety signal of thiopurine-induced injury of endothelial cells, essentially nodular regenerative hyperplasia, came from the use of 6-thioguanine.<sup>9</sup> Nodular regenerative hyperplasia was found thereafter in the French experience to constitute a non-exceptional long-term complication of treatment with thiopurines, particularly in males with previous extensive resection of the small bowel, leading in some cases to irreversible portal hypertension.<sup>10, 11</sup> Although the reality and the extent of this risk are still a matter of debate in other parts of the world, efforts have to be made in the near future to identify risk factors, clinical symptoms (splenomegaly, portal hypertension), biological surrogate markers (drop in platelet count, acquired cholestasis), non-invasive detection tools (MRI,<sup>12</sup> transient elastography<sup>13</sup>) and preventive measures (correction of folate and vitamin B<sub>12</sub> deficiency in patients with malnutrition or previous small bowel resection).<sup>11</sup>

Reactivation of hepatitis B and C under immunosuppressive treatment also represents a clinically challenging situation, even though concerning a minority of patients of IBD. The first step in addressing the problem is to identify patients at risk when initiating immunosuppressive treatment. Regarding this point, systematic hepatitis B virus (HBV) vaccination and serological testing before introducing immunosuppressive treatment have been recommended in the ECCO (European Crohn's and Colitis Organisation) guidelines on opportunistic infections, whereas no consensus could be reached for hepatitis C Virus (HCV) screening.<sup>14</sup>

The prevalence of patients with IBD at risk for reactivation of hepatitis has been clarified in a prospective cross-sectional nationwide Spanish study.<sup>15</sup> In this country, the prevalence of patients with IBD with hospital-based follow-up who

had biological markers of present and/or past HBV or HCV infection was 9.7%, a level similar to that of the local reference general population and lower than in previously published series. The authors also pointed out the low prevalence (12%) of patients with IBD with effective HBV vaccination, and observed that transfusion was no longer a significant risk factor for HCV infection as soon as HCV markers became mandatory in blood banks.

In this issue of *Gut* (see page 1340), the same Spanish REPENTINA group addressed the question of the prevalence and risk factors for liver dysfunction (LD) related to hepatitis B and C in patients with IBD receiving immunosuppressive treatment.<sup>16</sup> They identified from the previous study 104 patients with HBV markers (25 hepatitis B surface antigen (HBsAg) positive), 74 with HCV markers (51 HCV RNA positive) and 16 patients with markers of both infections, who have been treated at some time with immunosuppressive drugs. They retrospectively assessed in these patients the frequency and severity of LD according to exposure to one or more immunosuppressive drugs, with a median treatment time of ~1 year. The reader not familiar with the hepatology literature has first to be clear about consensual or adapted definitions of liver abnormalities in order to fully understand the results. According to an international classification based on biological tests alone,<sup>17</sup> 'abnormalities' of liver tests can be defined as an increase in aspartate transaminase, alanine transaminase (ALT), alkaline phosphatase (AP),  $\gamma$ -glutamyl transferase or total bilirubin between N (upper limit of the normal range) and 2N, whereas the terms 'liver injury' or 'hepatotoxicity' are proposed if there is an increase of >2 in the aforementioned liver tests. For the purpose of the study of hepatitis B and C in IBD, Loras *et al* proposed specific definitions for characterising three kinds of LD: viral reactivation or replication, acute liver failure and fulminant liver failure. For HBV, reactivation was defined as an increase of 1.5- to 2-fold compared with the baseline value of ALT plus an increase of >2000 IU/ml HBV DNA levels or DNA reappearance in a negative patient. HCV replication was defined as a significant increase in RNC-HCV or RNA reappearance in a negative patient plus an increase of 1.5- to 2-fold compared with the baseline value. LD related to immunosuppressive treatment in a HCV-infected patient was defined as a significant increase of ALT or HCV RNA virus load. Acute liver

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failure was defined as a sudden and severe impairment of liver function (bilirubin >2 mg/dl, albumin <34 g/l or prothrombin time <50%) and fulminant liver failure as severe acute failure complicated by hepatic encephalopathy.

The authors observed that 36, 24 and 0% of the 25 HBsAg-positive patients developed LD, hepatic failure or fulminant liver failure, respectively. Remarkably and unfortunately, only 6 of these 25 patients had received antiviral treatment before immunosuppression. No reactivation was found in antihepatitis B core antigen (HBc)-positive patients lacking HBsAg. Regarding HCV, viral reactivation was observed in only 16% of the 51 HCV RNA-positive patients, with one hepatic failure. To be treated with  $\geq 2$  immunosuppressive drugs (including steroids) was an independent predictor for HBV reactivation (OR 8.6). Of note, no reactivation was observed in patients receiving a monotherapy with azathioprine or infliximab together with a preventive antiviral treatment against HBV, and all the cases of liver failure occurred in patients receiving steroids alone or in combination with azathioprine or infliximab. No significant rate of progression towards cirrhosis was observed in either HBV or HCV infection. In summary, these original data are reassuring when considering initiating immunosuppressive drugs in HCV-infected patients. The same is true for HBV-infected patients receiving antiviral preventive treatment planned to be treated with a monotherapy by azathioprine or infliximab, but without additional steroids.

Most data on HBV under immunosuppression had been collected previously in patients receiving chemotherapy for haematological malignancies. A great merit of the Spanish study is the presentation of novel, valuable data on the effects of immunosuppression for IBD. Interestingly, the results seem to confirm the recommendations given by hepatological associations, based mainly on HBV reactivation with chemotherapy: recent practice guidelines by the AASLD (American Association

for the Study of Liver Diseases) and EASL (European Association for the Study of the Liver) and the German S3 guidelines recommend prophylactic antiviral treatment for hepatitis B carriers and agree that routine prophylaxis is not indicated for HBsAg-negative, but anti-HBc-positive patients.<sup>18–20</sup>

This Spanish cooperative study is also emblematic of a modern methodological approach for addressing safety concerns in very specific subgroups of patients. Premarketing clinical trials, postmarketing reporting and huge population-based cohorts without access to detailed individual stories are not able to provide this information. In contrast, cooperative cohorts adequately tailored for addressing pre-established questions have reasonable chances to successfully address some 'orphan' clinically relevant interrogations, and must be encouraged.

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