Journal of Crohn's and Colitis (2014) 8, 436–437

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## LETTER TO THE EDITOR

### Infliximab induced liver injury in Crohn's disease: A challenging diagnosis

*Dear Sir,*

A 24-year-old male patient with a 6-year history of Crohn's disease (A2L1B2, Montreal classification),[1] in remission for 4 years with mesalazine, was admitted in September 2010 complaining of abdominal pain and cramps. Physical examination revealed slight and diffuse abdominal pain. Entero-magnetic resonance revealed terminal ileitis and, thus, budesonide (9 mg/day) and azathioprine (2.5 mg/kg/day) were started. Nevertheless, the patient presented 12% of weight loss in 7 months. In April 2011, abdominal ultrasound showed persistent bowel loop wall thickening. Infliximab 5 mg/kg was added to azathioprine in May 2011 and the patient became rapidly asymptomatic, presenting 10 kg weight gain. However, since the second infliximab infusion, liver tests raised: ALP 388 U/L (NR: 38–126 U/L), GGT 339 U/L (NR: 12–58 U/L), AST 167 U/L (NR: 15–46 U/L), ALT 211 U/L (NR: 13–69 U/L). Azathioprine was interrupted in October 2011. Serological tests for hepatitis A, B and C, cytomegalovirus, Epstein–Barr virus and herpes simplex virus were negative. Liver autoimmunity and metabolic study, abdominal ecodoppler, computerized tomography and magnetic resonance cholangiopancreatography were all normal. A liver biopsy revealed slight, chronic hepatitis and cholestasis.

Considering the exclusion of main liver diseases (such as primary sclerosing cholangitis, nodular regenerative hyperplasia, autoimmune hepatitis, reactive hepatitis, hepatosplenic T cell lymphoma, viral hepatitis reactivation, cirrhosis), the temporal correlation between infliximab exposure and laboratorial changes, along with a CIOMS/RUCAM score of 8 (reflecting a probable toxic effect of infliximab on the liver),[2] an infliximab-induced hepatitis diagnosis was admitted. In December 2011, a switch to adalimumab was made and liver enzyme reached normal values in 8 months (Fig. 1).

Several drugs used to treat IBD have been implicated in liver injury, however, relatively few cases of anti-TNF-α induced hepatitis have been reported.[3] In this case, IBD related hepatobiliary diseases and malignancy were excluded. Withdrawal of azathioprine was the first option, since this drug is responsible for most of the cases of hepatotoxicity in IBD patients. However, liver enzymes remained elevated. As there was strong evidence of temporal relationship between infliximab exposure and elevation of liver enzymes, a switch to adalimumab was decided, enabling an uneventful recovery.

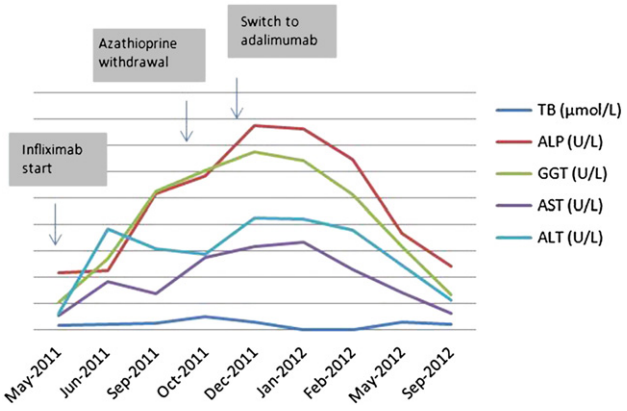


**Figure 1** Liver tests evolution since infliximab introduction until 8 months after its withdrawal. Abbreviations: TB: total bilirubin; ALP: alkaline phosphatase; GGT: gamma-glutamyltransferase; AST: aspartate aminotransferase; ALT: alanine aminotransferase.

Although rare, there are some case reports of infliximab induced liver injury. Autoimmune phenotype is the most common, but cholestatic pattern has also been reported.[4] Polymorphisms in genes encoding proteins related to TNF-α seem to modify pharmacodynamics of anti-TNF-α. This fact may explain different individual response to TNF-α antagonists and also distinct patterns of toxicity and absence of cross-reactivity between these drugs.[5]

Thus, DILI diagnosis can represent a clinical challenge in IBD patients, as it, following the exclusion of other causes, involves a temporal correlation between drug exposure and appearance of hepatic abnormalities, and its normalization after treatment withdrawal.

**Conflict of Interest:**

There are no financial or other relations that could lead to a conflict of interest.

## Acknowledgments

The authors did not receive any funding for this work.


http://dx.doi.org/10.1016/j.crohns.2013.11.013

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Joana Carvalheiro*
Sofia Mendes
Carlos Sofia
*Gastroenterology Department,*
*Centro Hospitalar e Universitário de Coimbra,*
*Coimbra, Portugal*
*Corresponding author.
*E-mail address:* joanameloc@gmail.com


11 November 2013