Infliximab-Associated Hepatic Injury in Crohn’s Disease

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Abstract

Hepatotoxicity disorders are relatively common in patients with inflammatory bowel disease that includes ulcerative colitis and Crohn’s disease. Abnormal serum liver functions tests can develop during treatment with (TNF-α) blocking agents, such as, Infliximab. The aim of this review is to clarify the role of infliximab in the development of liver enzyme abnormalities in patients with Crohn’s disease. The most common presentation of infliximab-associated liver injury is a hepatocellular type with auto-immune features, marked by increased serum aminotransferases levels. Cholestatic injury is much less common, and marked by jaundice and increased serum ALP and bilirubin levels, with elevations of serum ALT and AST. Abnormalities of liver function tests in sera of patients with Crohn’s disease typically resolve after discontinuation of infliximab, although severe liver injury leading to liver transplant cannot be ruled out.

Keywords: Aminotransferase, autoimmune hepatitis, Cholestatic, Crohn’s, hepatocellular, inflammatory bowel disease, Infliximab, liver.

Introduction

Crohn’s Disease: Crohn’s disease (CD) is a chronic inflammatory condition characterized by discontinuous skip lesions affecting any part of the gastrointestinal tract from the mouth to the anus. It is encompassed in the term “inflammatory bowel disease (IBD)”, which includes ulcerative colitis (UC) and CD1. Crohn disease is a chronic disease with an annual incidence ranging from 3 to 20 cases per 100,000. The median onset of disease is age 30 years and it has 2 peaks, first between age 20 and 30 years and then a smaller peak around age 50 years2. The origin of the disease is not entirely clear however several involved mechanisms have been postulated such as genetic predisposition and disruption of homeostasis regulation in the gastrointestinal tract3. The diagnosis and management of Crohn’s disease is based on clinical signs and symptoms in addition to laboratory tests, endoscopy and imaging techniques4. Medical treatment for IBD typically targets inflammatory mediators including aminosalicylates, corticosteroids, immunomodulators such as methotrexate, and the biological therapies including anti-tumor necrosis factor (TNF) therapies5. The aim of this review is to clarify the role of infliximab in the development of liver enzyme abnormalities in patients with CD and its relationship to drug-induced liver injury (DILI).

Anti-Tumor Necrosis Factor Alpha Therapy: Biologic therapy with anti-TNF medication has been effective in treating inflammation and reducing complications in CD6. Infliximab, adalimumab, and certolizumab have been shown to be effective as both induction and maintenance therapy in moderate to severe CD7. In systematic review of Singh S et.al. It has been suggested through indirect comparisons that infliximab or adalimumab may be preferred as the first line agents, while ustekinumab preferred as the second line agent, for induction of remission in patients with moderate-severe CD8. In (Robbins L. et al.) study, anti-TNF alpha therapy successfully treated denovo CD in 28 out of 38 (74%) patients. Out of seventeen patients with CD who had failed to response to anti-TNF alpha agents before surgery and were treated with anti-TNF alpha therapy after surgery, twelve patients (71%) responded to the treatment9. A study of Buhl S et.al. reported that in total, 376 Crohn’s disease patients had received infliximab. After 1 year of therapy 76 (20%) among them were classified as having response but non-remission. While it was found that there was no additional therapeutic
benefit after another year of treatment maintenance of infliximab for (n = 54; 71%), thus still having response but non-remission. Nineteen patients (25%) obtained remission during continued infliximab, whereas only 4% (n = 3) experienced treatment failure\(^\text{10}\). Loss of response LOR to biologics in Crohn’s disease is a significant clinical problem \(^\text{11}\). The rates of LOR are reported to be 50–54% in CD patients during 1 year of continuous IFX treatment \(^\text{12}\). The rates of LOR are reported to be 50–54% in CD patients during 1 year of continuous IFX treatment \(^\text{13,14}\). While in other study indicated by meta-analysis that the incidence of LOR among adult CD patients undergoing IFX therapy is 34% \(^\text{15}\). Study by de Bruyn JR et.al reported that the failure to Infliximab therapy is associated with subclinical fibrosis in Crohn’s disease \(^\text{16}\).

There are numerous complications which have been described with the use of infliximab such as instances of cholestasis or hepatitis \(^\text{45,47,50}\), induction of auto-immune/autoimmune-mediated hepatitis \(^\text{51-54}\), acute liver failure \(^\text{55,56}\) and the need for liver transplantation \(^\text{57,58}\). In the earlier controlled trial of Infliximab in Crohn’s disease minor elevation in levels of the liver enzymes were described, but extreme elevations were rare, and no cases of liver failure or jaundice were found \(^\text{21}\). Cholestatic liver injury was described in one case report of a patient treated with IFX. The patient developed jaundice after the infliximab infusion, with high alkaline phosphatase levels accompanied by elevations in bilirubin, ALT and AST. The patient underwent liver biopsy which revealed “bland cholestasis”. Cholestatic injury resolved within 4 weeks with supportive therapy and cessation of IFX \(^\text{47}\). Cases of AIH have also been demonstrated in patients with IBD receiving treatment \(^\text{38}\). Several cases have been reported AIH in CD patients who received infliximab therapy \(^\text{51-54,59}\). In one of these cases, Cravo et al.\(^\text{51}\) reported a 38-year-old female suffering from Crohn’s disease who required IFX. At the beginning of therapy, LFTs were normal, furthermore ANA as well as Anti-ds-DNA were negative. Importantly, 2 years into treatment with IFX, the patient developed transamnases and hyper gammaglobulinemia. Serology results for viral infections were negative, moreover ANA, Anti-ds-DNA, in addition to antihistone antibodies were positive. “Liver biopsy showed chronic hepatitis with inflammatory plasmocytic infiltrate in the portal tracts, interface hepatitis, and mild periportal fibrosis.”. So, the patient met the criteria for a definitive autoimmune hepatitis. During three-months period, after discontinuing IFX therapy, ANA titers reduced with normalization of LFTs \(^\text{51}\). In most reported cases of IFX-induced autoimmune hepatitis, the hepatitis resolved with discontinuation of infliximab and steroid treatment. Interestingly, in two of these reported cases, AIH resolved when switched to another biologic agent for exampleadalimumumab (ADA) implying an absence of cross-reactivity \(^\text{51,5}^3\). This phenomenon can be related to IFX being a chimeric (part mouse, part human) monoclonal antibody, while ADA is a fully human antibody \(^\text{22,51}\). In this regard, Rodrigues et al.\(^\text{50}\) described 8 cases of TNF-α blocking agents-induced hepatitis which was defined as ALT levels (>10× ULN) out of a cohort including 600 patients, with seven cases related to infliximab (3/7 patients with Crohn’s disease). These 3 patients with Crohn’s disease showed an autoimmune type of liver injury, with elevated levels of amionotransferases. Two patients responded favourably to steroids with normalization of LFTs after the suspension of IFX. In one female patient, IFX therapy was restarted within three months after discontinuation of this agent, with no recurrence of the liver injury \(^\text{60}\). In the case reports of van Casteren-Messidoro et al.\(^\text{59}\) two females patients suffering from IBD developed AIH while receiving IFX. One case with Crohn’s disease, developed AIH after the third infusion of IFX, with elevated serum transaminase levels up to (25 × ULN). During five-months period, after discontinuing IFX, and receiving azathioprine along with steroids, her transaminases normalized \(^\text{59}\). Crohn’s disease, chronic inflammatory granulomatous condition of gastrointestinal tract, can rarely have extra-intestinal complications. Involvement of the vulva in CD is very uncommon \(^\text{61}\). Causse et al.\(^\text{56}\) reported a case of IFX-induced acute hepatitis in a patient suffering from severe vulvar Crohn’s disease. Her LFTs showed ten times the normal value of ALT, twice the normal value of AST, 1.5 times the normal value of ALP and three times the normal value of GGT. Due to the hepatitis, the IFX therapy was withdrawn \(^\text{56}\). Importantly, the latest case reports have described two rare cases of IFX-induced autoimmune hepatitis in patients with Crohn’s disease that led to liver failure necessitating liver transplantation. One well-documented case by Estes et al., \(^\text{57}\) described markedly elevated levels of amionotransferases and bilirubin, 5 months after starting IFX. Similarly, in another report by Wong et al.\(^\text{58}\), one such case developed 3 months after starting infliximab, with abnormal LFTs, low albumin level and jaundice.
Conclusion

Infliximab-associated liver injury is still a potential concern in patients with Crohn’s disease. The most common presentation is a hepatocellular pattern of injury with auto-immune features, involving histologic changes which are similar to autoimmune hepatitis. This pattern marked by increased serum and AST levels. Cholestatic injury due to Infliximab is much less common, and marked by increased serum ALP and bilirubin levels, with elevations of serum ALT and AST. Symptoms generally include jaundice. In most cases, these patterns of injury improve and abnormalities in liver function tests typically resolve after discontinuation of infliximab, although severe liver injury leading to liver transplant cannot be ruled out.

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References


35. Parisi I, O’Beirne J, Rossi RE, Tschochatzis E, Manousou P, Theocharidou E, Hamilton M,


55. Haennig A, Bonnet D, Thebault S, Alric L.


