**SHORT REPORT**

Chronic hepatitis B reactivation following infliximab therapy in Crohn’s disease patients: need for primary prophylaxis

M Esteve, C Saro, F González-Huix, F Suarez, M Forné, J M Viver

**Background:** There is little information about the effect of infliximab on the clinical course of liver disease in Crohn’s disease patients with concomitant hepatitis B virus (HBV) infection. Theoretically, immunosuppression induced by infliximab will facilitate viral replication which could be followed by a flare or exacerbation of disease when therapy is discontinued. There are no specific recommendations on surveillance and treatment of HBV before infliximab infusion. Two cases of severe hepatic failure related to infliximab infusions have been described in patients with rheumatic diseases.

**Patients and methods:** Hepatitis markers (C and B) and liver function tests were prospectively determined to 80 Crohn’s disease patients requiring infliximab infusion in three hospitals in Spain.

**Results:** Three Crohn’s disease patients with chronic HBV infection were identified. Two of the three patients with chronic HBV infection suffered severe reactivation of chronic hepatitis B after withdrawal of infliximab therapy and one died. A third patient, who was treated with lamivudine at the time of infliximab therapy, had no clinical or biochemical worsening of liver disease during or after therapy. From the remaining 80 patients, six received the hepatitis B vaccine. Three patients had antibodies to both hepatitis B surface antigen (anti-HBs) and hepatitis B core protein (anti-HBc) with normal aminotransferase levels, and one patient had positive anti-hepatitis C virus (HCV) antibodies, negative HCV RNA, and normal aminotransferase levels. Except for the patients with chronic HBV infection, no significant changes in hepatic function were detected.

**Conclusions:** Patients with Crohn’s disease who are candidates for infliximab therapy should be tested for hepatitis B serological markers before treatment and considered for prophylaxis of reactivation using antiviral therapy if positive.

Infliximab is the treatment of choice for patients with moderately to severely active and fistulising Crohn’s disease (CD) which is unresponsive to conventional treatment. Its use is contraindicated in the presence of active infection. However, recommendations with respect to prevention and treatment of infection before infliximab infusion mainly refer to bacterial and opportunistic infections. There is scarce information about the effect of immunosupmodulatory drugs on the clinical course of liver disease in CD patients with concomitant hepatitis B virus (HBV) or hepatitis C virus (HCV) infection. To date, the available information suggested that HCV and HBV infection should not influence treatment strategies for CD. However, two cases of severe or fulminant B hepatitis related to infliximab therapy have been reported in patients with rheumatic diseases. More recently, a patient with chronic hepatitis B receiving lamivudine therapy requiring infliximab for ankylosing spondylitis showed no significant change in liver disease or viral replication.

We report three CD patients and concomitant chronic hepatitis B from a cohort of 80 CD patients treated with infliximab in three different hospitals in Spain. Two patients showed hepatitis B reactivation, with resolution of infection in one case and a fatal outcome in the other. The third patient, simultaneously treated with lamivudine, showed no clinical or biochemical effects on liver disease.

**Patients and Methods**

From January 2000 to July 2003, 80 CD patients (45 men, 35 women; mean age 38.2 years (range 14–80)) were treated with infliximab in three different hospitals in Spain. The number of infusions per patient ranged from 1 to 22. Hepatitis C and B markers were prospectively determined before the first infliximab infusion in two hospitals as part of the baseline assessment prior to infliximab treatment. In the third hospital, serum was prospectively obtained before every infliximab infusion and stored in the serum bank. Hepatitis C and B markers of all patients treated in this hospital were analysed in basal sera. Markers for HBV and HCV were identified using the following techniques: hepatitis B surface antigen (HBsAg), antibodies to hepatitis B surface antigen (anti-HBs), antibodies to hepatitis B core protein (anti-HBc), hepatitis B e antigen (HBeAg), antibodies to hepatitis B e antigen (anti-HBe), and anti-HCV were detected by the Roche (Roche Diagnostics, Basel, Switzerland) ELA method (Cobas Core II System), HCV RNA by the Roche PCR process (Cobas Amplipcr HCV Monitor Test, v 2.0), and HBV DNA by Diogene’s (Gaithesburg, Maryland, USA) Hybrid Capture II assay. Liver function tests were prospectively determined in the three hospitals before every infliximab infusion and two months after the last infusion. Aminotransferase levels (alanine aminotransferase (ALT), aspartate aminotransferase (AST)), alkaline phosphatase, gamma glutamyl transferase (GGT), and total bilirubin were measured by standard laboratory methods.

**Results**

Three of 80 patients had chronic hepatitis B at the time of infliximab infusion, one with active viral replication. The case...
reports of these three patients are described below in detail. Six more patients received the hepatitis B vaccine several months before infliximab treatment and anti-HBs levels higher than 100 mIU/ml were detected before the first infusion. Three patients showed positivity for both anti-HBs and anti-HBc with normal aminotransferase levels, suggesting spontaneous resolution of infection months or years before infliximab treatment. One patient had positive anti-HCV antibodies, negative HCV RNA, and normal aminotransferase levels. Except for patients with chronic hepatitis B infection, no significant changes in hepatic function were detected during infliximab therapy.

**Case No 1**

A 34 year old man was diagnosed with CD of the ileocaecal and sigmoid area in August 1990. He was treated with prednisone 70 mg/day and enteral nutrition, developing steroid dependence in the following six months. Mild hypertransaminasemia was recorded and attributed to enteral nutrition. He was given azathioprine 2.5 mg/kg/day in February 2001, and in May 2001 he developed a fistulous tract from the terminal ileum to the urinary bladder. Ciprofloxacin was added as maintenance treatment to avoid urinary sepsis, and infliximab was administered at a dose of 5 mg/kg with an induction regimen of three doses. Partial remission was observed but early relapse occurred and surgical resection of the intestinal segment was indicated. An additional infusion of infliximab 10 days before surgery was administered in order to reduce inflammation. Resection of 40 cm of the terminal ileum and of three fistulous ileovesceral tracts was performed. Two months later the patient experienced malaise and nausea. Blood analysis disclosed increased levels of serum ALT (2089 IU/l), AST (1561 IU/l), alkaline phosphatase (540 IU/l), gamma glutamyl transferase (GGT 165 IU/l), and total bilirubin (1.7 mg/dl). Mild hypoaalbuminaemia (32 g/l) and a decrease in prothrombin rate (75%) were also found and the patient was admitted to hospital. Abdominal ultrasonography was normal. Serum markers for hepatitis A virus, HCV, cytomegalovirus, Epstein-Barr virus, and herpes virus were negative. IgM anti-HBC antibodies and high serum HBV/DNA polymerase levels were detected (10 400 pg/ml). Archival analysis disclosed increased levels of serum ALT (67 IU/l) and AST (36 IU/l) which persisted in subsequent controls. HBsAg, IgG anti-HBc, HBeAg, and HBV DNA were positive, and anti-HBs, anti-HBe, and IgM anti-HBc were negative. Other causes of liver damage such as HCV and delta viruses were ruled out and liver biopsy, performed in February 2000, confirmed a diagnosis of chronic hepatitis B infection with mild portal and lobular activity without fibrosis. Liver biopsy, performed in February 2000, confirmed a diagnosis of chronic hepatitis B infection with mild portal and lobular activity without fibrosis. Lamivudine 100 mg daily was started two months later showing a good response with HBeAg seroconversion, HBV/DNA clearance, aminotransferase normalisation, and positive HBsAg, which still persist.

In November 2001, the patient experienced a relapse of CD with severe perianal disease and was treated with azathioprine 2.5 mg/kg/day. In July 2003, infliximab was added to the treatment—due to recurrence of perianal disease with repeated abscess formation—after abscess drainage and seton placement. Three doses of infliximab were administered followed by eight weeks of maintenance treatment (two additional doses), resulting in a complete and sustained response. Lamivudine was also maintained and no flare up of HBV infection was detected in blood analysis performed every two months.

**DISCUSSION**

A frequency of HBV and HCV as high as 24% has been reported in patients with CD, generally related to surgical procedures and blood transfusions. In our series of 80 patients treated with infliximab, a much lower prevalence rate than previously described was found (7.5% and 1.2%) for
HBV and HCV, respectively). Immunosuppressive drugs in chronically infected patients may lead to enhanced viral replication with exacerbation of hepatitis. Hepatitis rebound generally occurs after immunosuppression withdrawal and the magnitude of the hepatocellular response theoretically depends on the potency of the immunosuppressors. However, in spite of a potentially harmful effect of infliximab therapy on the course of viral hepatitis, there is little information about the influence of this treatment in the course of coexistent viral hepatitis in CD patients. In addition, there are no specific recommendations for viral hepatitis surveillance in this setting.

Our first two cases showed typical signs of HBV infection in patients receiving immunosuppressive therapy. Acute flare of hepatitis occurred 2–3 months after infliximab withdrawal. In the first case, recovery to a normal immune response produced HBV clearance and HBsAg seroconversion. In contrast, in the second case, extensive cytolysis occurred that led to hepatic failure and death. Lamivudine, a reverse transcriptase inhibitor, has been used with success in the treatment of chemotheraphy related HBV reactivation in patients with haematopoietic neoplasms and in transplant recipients, and it could be a therapeutic option in these patients. However, severe flare up, as was the case in patient No 2, with high levels of bilirubin at presentation, seems to be predictors of treatment failure. A similar scenario was described in two hematogenic patients treated with infliximab. In one case clear reactivation of HBV hepatitis was documented; in the other, who required liver transplantation, no evidence of either serological or histological reactivation of HBV was demonstrated. Both patients were treated with lamivudine and showed normalization of liver function tests and persistence of HBsAg.

In No case 3, lamivudine was effective in inducing HBsAg seroconversion and was used as primary prophylaxis of HBV reactivation when infliximab was added to azathioprine therapy. Such a preventive effect has also been demonstrated in a patient with chronic hepatitis B and ankylosing spondylitis requiring infliximab therapy. In addition, lamivudine, as primary prophylaxis for HBV reactivation, has been used with success in a small series of patients treated with potent immunosuppressors and more recently in a case control study performed in patients with allogenic haematopoietic stem cell transplantation. Unfortunately, data on the long-term benefits of lamivudine are limited and mutations in the polymerase gene may emerge as soon as 6–9 months after therapy, inducing lamivudine resistance. In lamivudine-resistant HBV mutants, adefovir dipivoxil is a therapeutic option and should be taken into account when long term infliximab therapy is foreseen.

Three additional patients in the present series had positive antibodies to HBV, suggesting past infection. Aminotransferase levels in these patients remained within the normal range before and after infliximab therapy. However, it is important to note that reactivation can also occur in anti-HBc positive HBsAg negative patients because HBV may persist even after serological recovery. Thus infliximab should be administered with caution in these patients and liver function tests should be closely monitored.

In conclusion, our finding of reactivation of hepatitis B in HBsAg positive patients emphasizes the need for careful monitoring of viral hepatitis infection in patients with inflammatory bowel disease requiring immunosuppressive therapy, particularly infliximab. Antiviral therapy (lamivudine or adefovir dipivoxil) should be administered to those patients requiring infliximab therapy who exhibit positive surface antigen (HBsAg) with or without active viral replication. In addition, hepatitis B vaccination should be routinely recommended in all CD patients at diagnosis.

ACKNOWLEDGEMENTS

The authors are grateful to Fernando Fernández-Bañares, MD, and Eduard Gabcé, MD, for their valuable suggestions.

Authors’ affiliations

M Esteve, M Forné, J M Viver, Department of Gastroenterology, Hospital Universitari Moltó de Terrassa, Terrassa, Catalonia, Spain
C Saro, Department of Internal Medicine, Hospital de Cabueñes, Gijón, Asturias, Spain
F González-Huix, Department of Gastroenterology, Hospital Josep Trueta, Girona, Catalonia, Spain
F Suarez, Department of Gastroenterology, Hospital Joan Canalejo, La Coruña, Spain

REFERENCES

Chronic hepatitis B reactivation following infliximab therapy in Crohn's disease patients: need for primary prophylaxis

M Esteve, C Saro, F González-Huix, et al.

*Gut* 2004 53: 1363-1365
doi: 10.1136/gut.2004.040675

Updated information and services can be found at:
http://gut.bmj.com/content/53/9/1363.full.html

*These include:*

**References**
This article cites 15 articles, 3 of which can be accessed free at:
http://gut.bmj.com/content/53/9/1363.full.html#ref-list-1

Article cited in:
http://gut.bmj.com/content/53/9/1363.full.html#related-urls

**Email alerting service**
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Topic Collections**
Articles on similar topics can be found in the following collections

Hepatitis B (58 articles)

**Notes**

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/