

Fulminant Hepatitis After Infliximab in a Patient with Hepatitis B Virus Treated for an Adult Onset Still's Disease

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ABSTRACT. Infliximab, a chimeric anti-tumor necrosis factor- α monoclonal antibody, has been demonstrated to be efficient and safe in patients with active rheumatoid arthritis and in the management of severe bouts of Crohn's disease. However, the safety of infliximab has not been evaluated in patients infected with hepatitis B virus. We report the case of a 28-year-old woman, with a positive hepatitis B virus surface antigen, who developed fulminant hepatitis 2 weeks after receiving a second infliximab infusion for a refractory adult onset Still's disease. (J Rheumatol 2003;30:1624-5)

Key Indexing Terms:

INFLIXIMAB

ADULT-ONSET STILL'S DISEASE

FULMINANT HEPATITIS

Infliximab, a chimeric anti-tumor necrosis factor- α monoclonal antibody, has been demonstrated to be efficient and safe in patients with active rheumatoid arthritis¹ and in the management of severe bouts of Crohn's disease². Whereas mild adverse events (e.g., headaches and nausea), upper respiratory tract infections^{1,3} and several cases of tuberculosis⁴ have been reported after infliximab infusions, liver abnormalities are much less common^{1,5,6}. However, the safety of infliximab has not been evaluated in patients infected with hepatitis B virus (HBV).

CASE REPORT

The patient, a young African woman with no previous medical history and no regular alcohol use, first experienced polyarthritis, myalgias, and a high spiking fever in July 1998. Nonsteroidal antiinflammatory drugs (NSAID) were ineffective, and she was empirically treated with oral prednisone at a daily dose of 60 mg from October 1998. In March 1999, she was admitted to our department and adult onset Still's disease (AOSD) was diagnosed according to the classification criteria⁷. Serum ferritin was 6750 mg/l (normal range: 10–200 mg/l), and the proportion of glycosylated iso-ferritin was 7% (50–80). Rheumatoid factors were negative, antinuclear antibodies (ANA) were detected at a titer of 1:160, and anti-double-strand DNA antibodies were negative. Liver tests showed no abnormalities but serotyping for HBV detected a positive hepatitis B surface antigen (HBsAg) with anti-HBc IgG and anti-HBe antibodies. No HBVDNA polymerase activity was

detectable. Tests for hepatitis C and for human immunodeficiency virus were negative. Ultrasound of the abdomen was normal. As the patient was refractory to methotrexate given in combination with high doses of steroids, to intravenous immunoglobulins, and also to intravenous cyclophosphamide, her polyarthritis remained very active, and she was confined to bed. In June 2000, she received a first infusion of 200 mg (3 mg/kg) of infliximab (cA2, Remicade, Centocor Inc, Malvern, PA, USA). Before the initiation of infliximab, alkaline phosphatase and bilirubin levels were within the normal range, aspartate aminotransferase (AST) concentration was 140 UI/l (normal range: 5–45 UI/l), and alanine aminotransferase (ALT) concentration was 100 UI/l (normal range: 5–40 UI/l). The results of the HBV tests were unchanged, and HBVDNA was still negative.

Immediate tolerance to infliximab was excellent and a few days after the first infusion, the patient's condition dramatically improved. Two weeks after the first infusion, AST concentration was 52 UI/l, and ALT concentration was 54 UI/l; the patient received a second infliximab infusion. At the same time, she was continuing to take 10 mg/day prednisone, 2 \times 550 mg/day of naproxen, 80 mg/day of trimethoprim, and 400 mg/day sulfamethoxazole for primary prophylaxis of *Pneumocystis carinii* pneumonia, a regimen she had been following for more than 6 consecutive months. Ten days after receiving the second infliximab infusion, the patient complained of sudden malaise, fever, and jaundice and developed a maculo-papular pruriginous rash and was then promptly referred to hospital. On admission, she had jaundice, a non-bullous erythroderma, and a temperature of 39°C. No hepatomegaly was found on clinical examination. She had normal white blood cell and platelet counts, ALT and AST levels were 30 times the normal level, conjugated bilirubin level was 248 mmol/l (normal < 30 mmol/l). The prothrombin time was 18 (normal 10–13 s), and the factor V rate was 38%. Tests were positive for HBsAg, anti-HBc (IgG type, IgM negative), and anti-HBe antibodies, and still negative for HBV DNA. Multiple laboratory tests were performed to exclude other causes of liver dysfunction including: hepatitis A, C, D, cytomegalovirus, herpes simplex virus, ceruloplasmin and a-1 antitrypsin levels, antibodies to smooth muscle or mitochondria, and paracetamolemia. ANA were positive at a titer of 1:320 with a homogeneous pattern, anti-dsDNA antibodies were negative. The erythema spontaneously resolved, but the patient's general status and consciousness rapidly declined. The patient fell into a profound coma requiring mechanical ventilation 4 days after admission. As the factor V level decreased below 10%, the total bilirubin concentration exceeded 500 mmol/l and creatine level rose to 33 mg/l with a marked

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acidosis (pH 7.15). The patient underwent an orthotopic liver transplant 5 days after being admitted.

On histological examination, the liver was atrophic with a diffuse centrolobular necrosis affecting more than 90% of hepatocytes and mild diffuse inflammatory infiltrate mainly due to neutrophils and eosinophilic mononuclear cells. Any underlying portal or periportal fibrosis was observed. No multinuclear hepatocytes nor cytoplasmic inclusion suggestive of a viral etiology were found. Modified orcein stain did not identify intracytoplasmic HBsAg. Immunostaining for the presence of herpes simplex 1 and 2 and cytomegalovirus was also negative. As HBV reactivation was first suspected, the patient was given 100 mg/day of lamivudine before transplantation and for one month afterwards and monthly infusions of specific anti-HBV immunoglobulins. One year after transplantation, liver tests were within the normal ranges and her serological status towards HBs was unchanged. Her polyarthritis was still very active despite a maintenance therapy with 10 to 15 mg/day oral prednisone and immunosuppressive therapy with both mycophenolate mofetil and FK506.

DISCUSSION

Although liver involvement is common in AOSD, life-threatening hepatic failure mimicking Reye's syndrome is extremely rare and tends to occur after high dose salicylate therapy or other NSAID⁸⁻¹⁰. In this case, it seems unlikely that naproxen contributed to the occurrence of hepatic failure. Indeed, the patient had been taking various NSAID including naproxen from 1998 with no history of hepatotoxicity. Moreover, the pathological findings did not look like those described in AOSD⁸⁻¹⁰. In the same way, sulfamethoxazole, which was given to the patient at a stable dose for more than 6 months, was unlikely to be involved by itself in the pathogenesis of hepatic failure.

Furthermore, we found no evidence for HBV reactivation nor for any other etiological factor. Lastly, the chronological relationship between the onset of hepatitis and infliximab infusion, which was somewhat surprising, provided strong evidence that infliximab was involved in this fulminant hepatitis. However, since more than 150,000 patients worldwide have already been treated with infliximab³ and no other cases of life-threatening hepatitis have been reported; thus this experience raises several hypotheses. Unlike previous reports of 2 cases of hepatitis following infliximab therapy^{5,6}, the hepatic process of the patient was not characterized by prominent biliary ductules damage, and anti-DNA antibodies were not associated with hepatitis⁶.

Whether AOSD patients have a particular predisposition to develop severe hepatitis after infliximab therapy cannot be assessed because only a small number of AOSD patients have been treated with this agent¹¹.

Infliximab may have indirectly facilitated sulfamethoxazole or even naproxen hepatotoxicity through an immunological mechanism that could also explain the initial erythrodermal rash. The patient's chronic HBV infection raises another hypothesis. There is evidence that hepatic expression of tumor necrosis factor- (TNF-) is increased in chronic HBV infection¹². Therefore, infliximab could have favored a sudden and massive intrahepatic release of TNF-, leading to liver destruction. The safety of TNF-

antagonists was recently assessed in a retrospective study of 12 patients with rheumatoid arthritis and chronic hepatitis C¹³ and in a patient with Crohn's disease¹⁴, but similar data in patients with chronic or acute HBV infection are lacking. As we cannot exclude any of the above hypotheses at this stage, and given the severity of the complication reported here, we think that infliximab should be used very cautiously in patients with positive HBsAg even in the absence of HBV replication or active hepatitis. In the absence of an alternative therapy, we suggest that HBsAg positive patients should be treated with oral lamivudine before receiving infliximab for their underlying inflammatory disease, and that they should be monitored closely for hepatic function.

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