Fulminant Liver Failure due to Hepatitis B Reactivation During Treatment With Tocilizumab

Milan J. Sonneveld, MD, PhD1, S. Darwish Murad, MD, PhD1, A.A. van der Eijk, MD, PhD2, and R.A. de Man, MD, PhD1

1Department of Gastroenterology and Hepatology, Erasmus MC University Medical Center, Rotterdam, The Netherlands
2Viroscience, Erasmus MC University Medical Center, Rotterdam, The Netherlands

ABSTRACT

Tocilizumab is a humanized monoclonal antibody targeting the interleukin-6 receptor that is frequently used for the treatment of refractory rheumatoid arthritis. Since patients with hepatitis B virus (HBV) infection were excluded from pivotal trials, the risk of HBV reactivation with this novel drug class remains uncertain. We present the first case of tocilizumab-associated HBV reactivation resulting in fulminant hepatic failure and a need for liver transplant. Our findings underscore the need for prophylactic antiviral therapy in patients being treated with novel immunosuppressive agents.

INTRODUCTION

Hepatitis B virus (HBV) reactivation is a serious and potentially fatal complication of immunosuppressive therapy. Current guidelines recommend screening for HBV markers in patients undergoing profound immunosuppression (eg, rituximab) and consideration of prophylactic therapy in patients at high risk. However, because HBV-infected patients are usually excluded from participation in clinical trials, the risk of HBV reactivation under emerging biologicals and novel immune modulators is largely unknown. Tocilizumab is a humanized monoclonal antibody targeting the interleukin-6 (IL-6) receptor. IL-6 is a proinflammatory cytokine that, among others, appears to have a major role in the pathogenesis of rheumatoid arthritis (RA). Tocilizumab has been shown to be very effective in patients with RA. Because IL-6 has a myriad of proinflammatory and antiviral properties, HBV reactivation is a potential concern with IL-6 antagonist therapy.

There is no consensus on the magnitude of the risk of HBV reactivation with tocilizumab. We present, to our knowledge, the first case report of tocilizumab-associated HBV reactivation resulting in fulminant liver failure, necessitating urgent liver transplantation.

CASE REPORT

A 59-year-old Chinese woman with a medical history of RA for which she had been primarily treated with methotrexate 10 years before presented to another clinic. At that time, she was also diagnosed with an HBeAg-negative chronic HBV infection for which she received no treatment. After 2 years, she developed an HBV flare after which methotrexate was discontinued. Liver biopsy showed minimal fibrosis. After the flare, she was again not treated with antiviral agents. Two years later, azathioprine and low-dose prednisolone were started for a new episode of active RA without any liver-related adverse events. One year before the current presentation, she was switched to a combination of leflunomide, hydroxychloroquine, and low-dose prednisolone (10–15 mg/d). At this time, she was still hepatitis B surface antigen (HBsAg) positive, with unknown HBV DNA levels. She became HBsAg negative during the follow-up and developed borderline positive anti-HBs. She was also immunoglobulin G positive for cytomegalovirus (CMV) without detectable viremia.

Unfortunately, her RA was insufficiently controlled and she was considered for treatment with tocilizumab. During screening, she was again HBsAg positive and anti-HBs negative and had an HBV DNA level of 88 IU/mL. Tocilizumab therapy was commenced with 8 mg/kg once every 4 weeks intravenously without concomitant prophylactic antiviral therapy based on the low viral load and perceived low risk of HBV reactivation with tocilizumab. Shortly after the start of tocilizumab, she developed a rapidly progressive hepatitis with a peak alanine aminotransferase (ALT) of 2,125 IU/L. At this time, she had an HBV DNA level of 3.6 × 10^6 IU/mL.

ACG Case Reports Journal / Volume 6 acgcasereports.com 1
Tocilizumab and leflunomide were discontinued, and she was started on entecavir 0.5 mg once daily. This resulted in a rapid decline of HBV DNA and ALT, but she developed marked jaundice (bilirubin 431 IU/L), coagulopathy (international normalized ratio 2.9), and grade 2 hepatic encephalopathy (Figure 1). She was subsequently transferred to our center for evaluation for liver transplantation. At the time of presentation, she complained of malaise, nausea, and vomiting. She was jaundiced and had asterixis and a grade 2 encephalopathy. Besides a distended abdomen with shifting dullness and mild peripheral edema, her physical examination was unremarkable. Additional biochemical investigations are shown in Table 1. She had no evidence of hepatitis A, C, D, or E infection but did have a detectable CMV polymerase chain reaction ($1.99 \times 10^4$ IU/L). Her HBV DNA level was $1.31 \times 10^3$ IU/mL. Imaging showed marked ascites without evidence of portal vein thrombosis, no evidence of biliary obstruction or malignancy, and no signs of cirrhosis. She was treated with valganciclovir and received antibiotic and antifungal therapy per the local protocol while entecavir was continued. Nevertheless, her health deteriorated and progressed to grade 3 encephalopathy. She was admitted to the intensive care unit and was listed for high urgency liver transplantation. She underwent an uncomplicated liver transplantation with a donation after brain death liver 5 days after. Posttransplant immunosuppression consisted of prednisolone, basiliximab (days 1 and 4), mycophenolate mofetil, and subsequently tacrolimus. She received anti-HBs immunoglobulin and entecavir posttransplant and was treated with valganciclovir until CMV DNA was undetectable. She remains well to this date, with her RA well controlled without additional RA medication. A pathological study of the explant showed a picture compatible with acute liver failure with completely distorted architecture and massive hepatic necrosis with ductular reaction. There was limited periportal fibrosis without evident cirrhosis. The findings were compatible with acute viral hepatitis but could also fit with toxic liver injury.

DISCUSSION

Current treatment guidelines for the management of patients with HBV infection suggest beginning prophylactic antiviral therapy in all HBsAg-positive patients, regardless of the HBV

**Figure 1.** An overview of ALT, bilirubin, HBV DNA, and INR. ALT, alanine aminotransferase; HBV, hepatitis B virus; Hydroxychl, hydroxychloroquine; INR, international normalized ratio; Lef, leflunomide; Pred, prednisolone; TOC, tocilizumab.
DNA level when undergoing profound immunosuppression. Because patients with HBV infection were excluded from pivotal trials, it has been unclear whether this recommendation should include patients treated with IL-6 receptor antagonists.

IL-6 has a myriad of proinflammatory and antiviral properties. Various studies have shown that IL-6 is upregulated in HBV-infected patients, IL-6 polymorphisms are associated with the clearance of HBV infection, and IL-6 also appears to have a role in hepatocarcinogenesis in HBV infected patients.5,6 Furthermore, IL-6 has also been shown to suppress HBV replication and to prevent the accumulation of HBV covalently closed circular DNA and HBV entry into hepatocytes.4,5 Despite the apparent importance of IL-6 for control of HBV infection, existing evidence has yielded contradictory results regarding the risk of HBV reactivation with tocilizumab. In a case report from 2008, Nagashima and Minota described a single HBeAg-positive patient who was treated with tocilizumab without any apparent issues.6 Furthermore, Chen et al studied 63 patients treated with tocilizumab, 49 of whom had evidence of (chronic or resolved) HBV infection.7 Three of 7 untreated HBsAg-positive patients developed HBV reactivation, whereas none of 41 HBsAg-negative, anti-HBc-positive patients experienced reactivation.8 Our case shows that HBV reactivation during tocilizumab can also cause severe hepatitis with subsequent fulminant liver failure.

It is important to note that tocilizumab itself has also been implicated as a cause of toxic liver injury. In the registration trials, up to 71% of patients experienced modest increases in ALT during treatment, with ALT elevations over 5 times the upper limit of normal reported in 2%.1 There are at least 2 case reports of severe liver toxicity attributed to tocilizumab.9,10 Although it is impossible to conclusively determine the cause of liver failure in our patient, the course of events (development of an HBV DNA flare with subsequent hepatitis and resolution of hepatitis upon commencing antiviral therapy) suggest HBV reactivation as the primary cause. Concomitant toxic liver injury can, however, not be completely excluded. The role of CMV in the current clinical scenario is also unclear. CMV reactivation may occur in the context of acute hepatitis because of other causes, but CMV-related liver disease has been reported with tocilizumab and thus may have contributed to the rapid deterioration of liver function in our patient.11

In conclusion, we report the first case of tocilizumab-associated HBV reactivation resulting in liver failure and a need for liver transplantation. Our case underscores the need to consider prophylactic antiviral therapy in all HBsAg-positive patients undergoing IL-6 receptor antagonist therapy.

Table 1. Laboratory findings at the time of transfer to our liver unit

| Assay           | Result   | Normal values     |
|-----------------|----------|-------------------|
| Hemoglobin      | 7.3 mmol/L | 7.5–9.5          |
| Leukocytes      | 13.0 × 10^9/L | <10             |
| Thrombocytes    | 166 × 10^9/L | 150–370         |
| Glucose         | 5.5 mmol/L | 4.0–6.1          |
| Urea            | 2.4 mmol/L | 2.5–7.5          |
| Creatinine      | 54 mmol/L | 55–90            |
| Ammonia         | 58 μmol/L | <45              |
| Albumin         | 22 g/L    | 35–50            |
| IgG             | 13.6 g/L  | 7.0–16.0         |
| CRP             | 21 mg/L   | <30              |
| AST             | 149 U/L   | <31              |
| ALT             | 130 U/L   | <34              |
| LDH             | 746 U/L   | <247             |
| Alkaline phosphatase | 277 U/L | <98              |
| Bilirubin       | 365 umol/L | <17             |
| INR             | 2.4       | <1               |
| Factor V        | 0.34      | 0.50–1.50        |
| ANA             | Negative  | Negative         |

ALT, alanine aminotransferase; ANA, antinuclear antibody; AST, aspartate aminotransferase; CRP, C-reactive protein; IgG, immunoglobulin G; INR, international normalized ratio; LDH, lactate dehydrogenase.
DISCLOSURES
Author contributions: All authors contributed equally to this manuscript. MJ Sonneveld is the article guarantor.

Financial disclosure: None to report.

Informed consent was obtained for this case report.

Received April 13, 2019; Accepted September 11, 2019

REFERENCES
1. Scott LJ. Tocilizumab: A review in rheumatoid arthritis. Drugs. 2017;77:1865–79.
2. Lan T, Chang L, Wu L, Yuan YF. IL-6 plays a crucial role in HBV infection. J Clin Transl Hepatol. 2015;3:271–6.
3. Xia C, Liu Y, Chen Z, Zheng M. Involvement of interleukin 6 in hepatitis B viral infection. Cell Physiol Biochem. 2015;37:677–86.
4. Kuo TM, Hu CP, Chen YL, et al. HBV replication is significantly reduced by IL-6. J Biomed Sci. 2009;16:41.
5. Bouezzedine F, Fardel O, Gripon P. Interleukin 6 inhibits HBV entry through NTCP down regulation. Virology. 2015;481:34–42.
6. Nagashima T, Minota S. Long-term tocilizumab therapy in a patient with rheumatoid arthritis and chronic hepatitis B. Rheumatology (Oxford). 2008;47:1838–40.
7. Chen LF, Mo YQ, Jing J, Ma JD, Zheng DH, Dai L. Short-course tocilizumab increases risk of hepatitis B virus reactivation in patients with rheumatoid arthritis: A prospective clinical observation. Int J Rheum Dis. 2017;20:859–69.
8. Papalopoulos I, Fanourakis A, Kougkas N, et al. Liver safety of non-tumour necrosis factor inhibitors in rheumatic patients with past hepatitis B virus infection: An observational, controlled, long-term study. Clin Exp Rheumatol. 2018;36:102–9.
9. Anger F, Wiegering A, Wagner J, et al. Toxic drug-induced liver failure during therapy of rheumatoid arthritis with tocilizumab subcutaneously: A case report. Rheumatology (Oxford). 2017;56:1628–9.
10. Hiura M, Abe S, Tabaru A, et al. Case of severe liver damage after the induction of tocilizumab therapy for rheumatoid vasculitis. Hepatol Res. 2011;41:492–6.
11. Komura T, Ohta H, Nakai R, et al. Cytomegalovirus reactivation induced acute hepatitis and gastric erosions in a patient with rheumatoid arthritis under treatment with an anti-IL-6 receptor antibody, tocilizumab. Intern Med. 2016;55:1923–7.