Hepatitis B reactivation in a patient with rheumatoid arthritis with antibodies to hepatitis B surface antigen treated with rituximab.

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Abstract:
Hepatitis B virus (HBV) can still be found within the hepatocytes after its clearance and the control of viral replication depends on the immune response. However during immunosuppression, seroconversion of HBsAg has been described followed by disease reactivation. Hepatitis B virus reactivation represents an emerging cause of liver disease in patients undergoing treatment with biologic agents and in particular, by the use of rituximab (anti-CD20) and alemtuzumab (anti-CD52) that cause profound and long-lasting immunosuppression. We describe a case of a 64-year old female patient with rheumatoid arthritis and resolved HBV infection, who experienced a severe hepatitis B reactivation after the administration of rituximab.

Keywords: HBV reactivation, rituximab, rheumatoid arthritis, monoclonal antibodies

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Introduction
Approximately 2 billion people have been infected with hepatitis B virus (HBV) worldwide, with more than 350 million having chronic hepatitis B. Chronic HBV carriers have a 15-40% lifetime risk of developing serious complications of chronic liver disease1,2. The prevalence of chronic hepatitis B (CHB) among patients with rheumatic diseases is not greater than expected based on data from the general population in the same geographic area3.

The HBV infection triggers a reaction of the immune system of the host, developing antibodies (anti-HBs) and clearing the virus from the hepatocytes. Thus persons who become HBsAg-negative usually develop antibodies and can be considered to have resolved hepatitis B. However, a small proportion of these persons, is found to have detectable HBV DNA in serum, although the levels are low and observed only intermittently. This state has been referred as occult or latent hepatitis B and in this respect the disease may be reactivated by severe immunosuppression4,5.

HBV reactivation represents an important medical issue in HBV-infected patients treated with rituximab. Thus the identification of high-risk patients with active, inactive or occult HBV infection and the use of prophylactic antiviral treatment is crucial6. However, other reports showed that a low HBV (2%) reactivation was observed in patients with HBsAg/antiHBe positive and with B-cell lymphoma, receiving rituximab-based combination chemotherapy without concomitant antiviral prophylaxis7.

The developing hepatitis due to reactivation in many cases is quite severe, with a morbidity ranging from 5% to 40%8,9.

One of the most potent immunosuppressive drugs is rituximab, a chimeric antibody targeting the CD-20 receptor of the mature normal and abnormal B-lymphocytes resulting to their destruction. This agent is being used in non-Hodgkin lymphoma, in chronic lymphocytic leukaemia and, since 2006, in rheumatoid arthritis. References regarding reactivation of hepatitis B using rituximab in hematologic patients is abundant, whereas in rheumatoid arthritis the experience is rather limited. In this paper, we present a case of HBV reactivation, in a patient with rheumatoid arthritis treated with rituximab.

Case report
A 64-year-old female patient with rheumatoid arthritis was transferred to the Liver Unit from the Clinical Immunology Unit of the Internal Medicine Department in March 2011, due to elevated aminotransferases and the appearance of positive HBsAg, 2 years after the initiation of treatment with rituximab and methotrexate. She was diagnosed with rheumatoid arthritis since 2000 and from 2000 to 2008 she was treated with different agents i.e.
azathioprine, saloprine, cyclosporine and leflunomide.
Since January 2009 and for two consecutive years, her
treatment had been modified to methotrexate (5 mg every
Saturday and Sunday) and rituximab (2 doses of 1000 mg
with 15 days interval from dose to dose, per session -
such sessions were repeated every 6 months).
The patient was known to have a resolved hepa-
titis B. During these years, she was regularly screened
for aminotransferases and hepatitis serological markers
since she was receiving immunosuppressive drugs (Table
1). In February of 2011, there was an increase in ALT
and a seroconversion of HBsAg(-) to HBsAg (+). A few
days later (March 2011), there was a further increase of
aminotransferases levels (AST 246 U/ml, ALT 605 U/ml)
and HBsAg, anti-HBs, HBeAg and anti-HBc were posi-
tive with negative anti-HBe and core IgM. At her admis-
sion to our Unit, the patient was asymptomatic, the liver
and spleen were impalpable and there were no signs of
decompensation. During her hospitalization, she under-
went liver biopsy, all drugs were withdrawn and she un-
derwent antiviral therapy with 1 mg entecavir.

The HBVDNA levels were very high (> 1,1*10^8 IU/
ml) whereas HBcAb-IgM were negative. The liver biopsy,
performed in May 2011, showed severe impairment of the
liver architecture due to chronic hepatitis, with moderate
degree of fibrosis and extensive steatosis. According to the
biopsy report, this image was consistent with reactivation
of hepatitis B and extensive use of hepatotoxic drugs i.e. methotrexate and rituximab.

Discussion
Rituximab is a chimeric monoclonal antibody which
binds to the CD-20 receptors of B-lymphocytes. Rituxi-
mba leads to transient but almost complete depletion of
B cells in the blood and only partial depletion in the bone
marrow and synovial tissue. Since the B-cells secrete cy-
tokines and antibodies and act as antigen presenting cells,
their destruction disrupts both the innate and adaptive im-
une response.

The current licensed indication of rituximab is in
patients with rheumatoid arthritis who qualify for treat-
ment with biological agents. Patients with rheumatoid
arthritis on rituximab should be prescreened for Hepatitis
B and C. Patients with negative HBsAg but positive for
anti-HBc are allowed rituximab therapy if negative for
HBVDNA. While cases of HBV reactivation are widely
described in the oncology literature, only one case report
of HBV reactivation in a patient with rheumatoid arthritis
treated with rituximab has been reported 10.

In the reported clinical case, the patient with resolved
hepatitis, who was treated with rituximab, developed a
reactivation of HBV infection, with seroconversion of
HBsAg, anti-HBC and positive HbeAg, high aminotrans-
ferases levels and high viral load. Interestingly, anti-HBs
remained positive and increased at levels over 1000mIU/
ml after 6 months. Another significant finding was the ex-
tended damage of the liver consistent to chronic hepatitis,
severe degree of fibrosis and steatosis probably due to the
use of hepatotoxic drugs i.e. methotrexate and rituximab.
Intervention by antiviral treatment immediately after the
diagnosis of HBV reactivation and stopping biologic
treatment resulted in the control of HBV infection within
a few months with gradual decline of aminotransferases
Occult hepatitis B reactivation is an emerging concern in patients treated with monoclonal – antibody containing regimens and a serious cause of liver-related morbidity and mortality. Recent studies suggest that antiviral prophylaxis should be provided to HBsAg-negative and anti-HBe+ and /or anti-HBs-positive patients undergoing immunosuppressive treatment, if they are anti-HBs negative and if close monitoring of HBVDNA is not guaranteed. However EASL clinical practice guidelines recommend that these patients should be followed carefully by means of ALT and HBVDNA testing and treated with nucleos(t)ides upon confirmation of HBV reactivation before ALT elevation.

As the host immune response plays a pivotal role in controlling HBV infection, suppression of immune responses would increase viral replication. It is now known that the liver damage due to HBV reactivation is a 2-stage process. Initially during intense cytotoxic or immunosuppressive therapy there is a marked enhanced viral replication as reflected by increase in serum levels of HBVDNA, HBeAg and HBVDNA polymerase, resulting in widespread infection of hepatocytes. On the subsequent restoration of immune function due to withdrawal of cytotoxic or immunosuppressive therapy, there is a rapid immune-mediated destruction of HBV-infected hepatocytes, which is manifested clinically as hepatitis, hepatic failure and even death. Thus, as hepatitis due to HBV reactivation is preceded by enhanced HBV viral replication, a high prechemotherapy viral load is the most important risk factor for postchemotherapy HBV reactivation. In HBsAg-negative patients suspected to have HBV reactivation testing for HBVDNA should be performed more closely and antiviral treatment promptly needs to be added.

Conflict of interest
Authors declare no conflict of interest.

References