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

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. She was diagnosed with rheumatoid arthritis since 2000 and from 2000 to 2008 she was treated with different agents i.e.
azathioprine, salopyrine, 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 hepatitis 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, HBeAg and anti-HBe were positive with negative anti-HBc and core IgM. At her admission to our Unit, the patient was asymptomatic, the liver and spleen were impalpable and there were no signs of decompensation. During her hospitalization, she underwent liver biopsy, all drugs were withdrawn and she underwent antiviral therapy with 1 mg entecavir.

The HBVDNA levels were very high (> 1,1x10^8 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.

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 > 1000mIU/ml. In November of 2011, the anti-HBe became positive. At that time point we recommended the patient to continue the antiviral therapy with entecavir for one more year. The patient was symptom-free from her rheumatoid arthritis without any treatment.

### Discussion

Rituximab is a chimeric monoclonal antibody which binds to the CD-20 receptors of B-lymphocytes. Rituximab 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 cytokines and antibodies and act as antigen presenting cells, their destruction disrupts both the innate and adaptive immune response.

The current licensed indication of rituximab is in patients with rheumatoid arthritis who qualify for treatment 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.

In the reported clinical case, the patient with resolved hepatitis B, who was treated with rituximab, developed a reactivation of HBV infection, with seroconversion of HBsAg, anti-HBc and positive HbeAg, high aminotransferases 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 extended 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.

### Table 1: Progression of patient’s parameters by time.

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<tr>
<td>AST (U/ml)</td>
<td>32</td>
<td>246</td>
<td>249</td>
<td>501</td>
<td>52</td>
<td>26</td>
<td>19</td>
<td>16</td>
<td>18</td>
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<td>ALT (U/ml)</td>
<td>39</td>
<td>70</td>
<td>605</td>
<td>423</td>
<td>565</td>
<td>71</td>
<td>17</td>
<td>14</td>
<td>19</td>
<td>15</td>
<td>13</td>
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<td>γGT (U/ml)</td>
<td>25</td>
<td>154</td>
<td>323</td>
<td>346</td>
<td>127</td>
<td>72</td>
<td>47</td>
<td>39</td>
<td>29</td>
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<tr>
<td>HBVDNA(*)</td>
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<td>1,1x10^8</td>
<td>4,62x10^4</td>
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<td>HBsAg</td>
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<td>anti-HBs(**)</td>
<td>+</td>
<td>+</td>
<td>76,53</td>
<td>102,89</td>
<td>+</td>
<td>&gt;1000</td>
<td>658</td>
<td>292</td>
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<td>HBeAg</td>
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<td>anti-HBc</td>
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<td>anti-HBc IgM</td>
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(*): IU/ml, (**): mIU/ml, (#): Administration of rituximab (1/2009).
to normal levels, HBVDNA levels decline and seroconversion to HBsAg(-), HBeAg(-), anti-HBe(+).

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