CASE REPORT

Elevation of the Hepatitis B Virus DNA during the Treatment of Polycythemia Vera with the JAK Kinase Inhibitor Ruxolitinib

Keita Kirito¹, Minoru Sakamoto² and Nobuyuki Enomoto²

Abstract

Ruxolitinib is a useful treatment option for myelofibrosis since it effectively resolves splenomegaly and constitutional symptoms. After the widespread use of ruxolitinib outside of clinical trials, a series of case reports indicated a potential risk of ruxolitinib-associated opportunistic infections, including the reactivation of the hepatitis B virus (HBV). We herein report the case of a polycythemia vera patient who showed an elevation of HBV-DNA viral DNA with an elevation of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) after the initiation of ruxolitinib. Anti-viral therapy with entecavir was immediately started and the HBV viral load thereafter decreased with an improvement of the liver function. Physicians should thus be aware of the potential risk of ruxolitinib-associated HBV reactivation.

Key words: polycythemia vera, ruxolitinib HBV reactivation

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Introduction

Ruxolitinib is an inhibitor of Janus kinase subtypes 1 and 2 (JAK1 and JAK2), and it was first approved by the United States Food and Drug Administration (FDA) for the treatment of primary and post polycythemia vera (PV)- or post essential thrombocythemia (ET)-myelofibrosis (MF). Ruxolitinib effectively reduced splenomegaly, relieved constitutional disease symptoms and improved the overall survival of patients with MF (1). In addition to MF, the clinical investigation of ruxolitinib for the treatment of polycythemia vera is ongoing.

Recently, a series of case reports identified a potential association between ruxolitinib therapy and the development of severe infections, such as disseminated tuberculosis (2), Cryptococcus neoformans pneumonia (3) and bilateral toxoplasmosis retinitis (4). Additionally, two groups reported a patient with myelofibrosis who experienced a reactivation of hepatitis B virus after ruxolitinib treatment (5, 6).

In the present paper, we report the case of a patient with polycythemia vera who demonstrated an elevation of hepatitis B viral infection associated with a marked increase in the alanine aminotransaminase (ALT) levels after short-term exposure to ruxolitinib.

Case Report

A 64-year-old woman with polycythemia vera who had been treated with hydroxyurea was enrolled in a clinical trial for ruxolitinib (RESPONSE trial, Funded by Incyte and others; RESPONSE ClinicalTrials.gov number, NCT 01243944.) (7) after obtaining written informed consent. This study is approved by the institutional review board of our institution. We obtained the permission for this case report from the sponsored company and institutional review board (IRB). We also obtained the written informed consent from the patient.

She was known to have chronic hepatitis B infection. Serological testing at the trial onset indicated the presence of hepatitis B (HBs) antigen, anti-HBe antibody and anti-HBc antibody, but HBs antigen was undetectable. The serum
The serum levels of transaminase and the HBV-DNA copy numbers during the treatment.

Figure.

The serum levels of transaminase and the HBV-DNA copy numbers during the treatment.

hepatitis B virus (HBV)-DNA levels were 5.4 log copies/mL. The ALT levels remained within the normal limits for several years before the initiation of the study. Based on these data, we diagnosed her to have HBe-antigen negative chronic hepatitis B.

We determined that she did not have active hepatitis and decided that she would be suitable to participate in the clinical trial with careful monitoring of her ALT and HBV-DNA levels. Initially, she was assigned to the best available therapy group and continuously received treatment with hydroxyurea. Her ALT levels remained in the normal range and the HBV-DNA levels ranged between 5.5 to 6.0 log copies/mL during the treatment with hydroxyurea (Figure). After 6 months, the patient showed no improvement in hematocrit and splenomegaly, then the patient was crossed over to the ruxolitinib arm of the study and began receiving ruxolitinib at a dose of 10 mg/kg twice daily. At this time point, it had not been known that ruxolitinib had a potential risk for reactivation of HBV, thus we did not use any antiviral prophylaxis.

The ALT and aspartate aminotransferase (AST) levels at the start of ruxolitinib were within the normal range. Four weeks later, she was found to have a marked elevation of her ALT levels to 352 U/L and her HBV-DNA copy number (7.2 log copies/mL). Since the patient showed more than a one log (10 fold) elevation of HBV-DNA compared to the baseline along with a transaminase elevation, we concluded that our patient had experienced a reactivation of HBV infection according to the report by Yeo et al. (8). The genotype of her HBV virus was C, and a mutational analysis revealed that the virus isolated from the patient had both precore and core-promoter mutations. Ruxolitinib was immediately stopped, and antiviral therapy with entecavir was started. Two weeks later, her HBV-DNA levels were markedly reduced to 3.6 log copies/mL, and her liver transaminase levels improved as well (Figure).

Discussion

A re-activation of the hepatitis B virus is frequently observed and it is thought as one of the most serious problems in associated with cancer treatment. The risk of a reactivation of HBV in cancer patients depends on multiple factors, such as the state of HBV infections, the HBV-DNA copy number, the type of malignancy, and the immunosuppressive activity of the anti-cancer drugs (9). Interestingly, recent studies have highlighted the potential immunosuppressive effect of the JAK1/JAK2 inhibitor ruxolitinib. Ruxolitinib possibly suppresses the immune system through the inhibition of the actions of interferon γ and interferon α/β (10). Furthermore, an in vitro/in vivo study by Heine A et al. demonstrated that ruxolitinib blocks the function of dendritic cells (DC) and impairs the T-cell mediated immunity (11). It is well established that both DC and T-cells play essential roles in the defense against HBV infection (12).

The above findings suggested that ruxolitinib may therefore play a role in the reactivation of HBV. However, the reactivation of HBV after ruxolitinib is relatively rare event. Although ruxolitinib was used in two relatively large clinical trials (13, 14) for myelofibrosis and also used in outside clinical trials in United States and European countries since 2011, only two cases with HBV reactivation have so far been reported as summarized in Table. The first case was reported by Caocci and colleagues (5). The patient had post-essential thrombocythemia MF and developed a reactivation of HBV after 4 weeks of treatment with ruxolitinib. The patient had a history of HBV hepatitis and was also positive for HBs-Ag at the initiation of ruxolitinib treatment. In spite
of the elevation of HBV-DNA, the patient showed no increase in AST and ALT, thus no anti-viral medication was required. The second case was reported by Shen et al. (6). The patient was a HBV carrier before starting of ruxolitinib. This patient showed an elevation of ALT and HBV-DNA at 8 months after the initiation of ruxolitinib treatment. After the treatment with entecavir was started, the patient showed an improvement in his liver function and the HBV-DNA level decreased to the normal range. In contrast to these two patients, our patient showed a relatively aggressive clinical course, a rapid increase of HBV-DNA copy number after the initiation of ruxolitinib with a significant elevation of the liver transaminase levels. We do not have a precise explanation why our patient showed a rapid increase in the HBV-DNA copy number, however, the genotype of HBV virus or the presence of a gene mutation of HBV genome might have affected the clinical course. Borentain et al. reported that the non-A phenotype of HBV virus and the existence of core and/or pre-core mutation of HBV gene were associated with tendency for the reactivation of HBV to occur (15). Furthermore, it was reported that core/pre-core mutation was associated with the severity of hepatitis (16). Altogether, it is suggested that ruxolitinib may carry a potential risk of triggering HBV reactivation. As the prevalence of HBV infection in Asian countries including Japan is significantly higher than that in European countries and the United States (17), clinicians, especially in Asian countries, must be made aware of the potential risk of the hepatitis B virus reactivation associated with ruxolitinib administration. It should also be noted that in Asian countries, the prevalence of non-A genotype virus and core/precore mutation is higher than that of European countries and the United States (18). These factors could also be potential risk factors for HBV reactivation in ruxolitinib treated patients in Asian countries.

The careful assessment of HBV infection is therefore required before starting ruxolitinib and the careful monitoring of HBV markers and prophylaxis might be required for any patients that demonstrate an HBV infection during the treatment course as suggested by Heine et al. (19).

We obtained the permission for this case report from the sponsored company and IRB. We also obtained the written informed consent of the patient.

### Table. List of Patients Who Developed HBV Reactivation during Treatment with Ruxolitinib.

<table>
<thead>
<tr>
<th>age</th>
<th>sex</th>
<th>disease</th>
<th>status of HBV infection*</th>
<th>serological test for HBV *</th>
<th>HBV-DNA levels*</th>
<th>does of ruxolitinib</th>
<th>duration to HBV reactivation</th>
<th>Treatment</th>
<th>reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>49</td>
<td>W</td>
<td>post-ET MF</td>
<td>previous history of HBV hepatitis</td>
<td>HBsAg+, HBs-Ab+, HBc-Ab+, HBeAg-, HBe-Ab+</td>
<td>not detected</td>
<td>20mg BID</td>
<td>4 weeks</td>
<td>none</td>
<td>5</td>
</tr>
<tr>
<td>72</td>
<td>M</td>
<td>post-ET MF</td>
<td>HBV carrier</td>
<td>not available</td>
<td>not available</td>
<td>20mg BID</td>
<td>8 months</td>
<td>entecavir</td>
<td>6</td>
</tr>
<tr>
<td>63</td>
<td>F</td>
<td>post-PV MF</td>
<td>HBsAg- antigen negative chronic hepatitis B</td>
<td>HBsAg+, HBs-Ab+, HBc-Ab+, HBsAg- , HBc-Ab-</td>
<td>5.4 log copies/mL</td>
<td>20mg BID</td>
<td>4 weeks</td>
<td>entecavir</td>
<td>Present case</td>
</tr>
</tbody>
</table>

* prior ruxolitinib initiation

### References

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