Review Article

Hepatitis B and Hepatitis C Reactivation in the Biologic Era

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Abstract

Hepatitis B (HBV) and hepatitis C (HCV) reactivation may occur after the use of biologic agents. During the last decade, utilization of biologics has changed the fate of many treated for cancer, autoimmune and connective tissue disease, maintenance of transplanted organs, and the prevention of graft-versus-host disease among others. HBV reactivation has been reported in up to 50% of HBV carriers undergoing immunosuppressive therapy, and there is emerging data pointing towards an increased risk for HCV reactivation. If reactivation of HBV and HCV occurs, the spectrum of clinical manifestations can range from asymptomatic hepatitis flares to hepatic decompensation, fulminant hepatic failure, and death. Therefore, identifying patients at risk and early diagnosis are imperative to decrease significant morbidity and mortality. The purpose of this article is to review the pathophysiology of the reactivation of HBV and HCV infection in patients receiving biologic therapies and the approaches used to diagnose, prevent, and treat HBV and HCV reactivation.

Introduction

Chronic hepatitis B (HBV) and C virus (HCV) infection are major causes of morbidity and mortality in the United States (US). It is estimated that approximately 1.3 million and 5.2 million people in the US suffer from chronic HBV and HCV infection, respectively.[1,2] Both chronic infections can lead to cirrhosis, hepatocellular carcinoma, and liver transplantation. During the last decade, screening guidelines for HBV and HCV have improved to assist in the recognition of populations at higher risk (Table 1).

With unprecedented advances in the treatment against cancer, autoimmune and connective tissue diseases,

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transplantation, and the prevention of graft-versus-host disease, data are emerging that point towards an increased risk of HBV and HCV reactivation after the use of biologics. HBV reactivation has been reported in 20% to 50% of HBV carriers undergoing immunosuppressive therapy or chemotherapy.[3–6] The spectrum of clinical manifestations can range from asymptomatic hepatitis flares to hepatic decompensation, fulminant hepatic failure, and death. In contrast, HCV reactivation is rare, but if severe hepatitis develops, the mortality rates are similar to that of HBV infected patients.[7–13] Some of the biologics identified to increase the risk of HBV and HCV reactivation include monoclonal antibodies to T and B cells. These include rituximab, alentuzumab, and tumor necrosis factor (TNF)-α antagonist with or without combination therapy (including corticosteroids).[14–29]

Here, we review the pathophysiology of the reactivation of HBV and HCV in patients receiving biologic therapy and provide approaches for the diagnosis, prevention, and treatment of HBV and HCV reactivation.

Hepatitis B reactivation

The natural course of HBV infection is determined by the interplay between virus, host, and environment.[30] The rate of progression from acute to chronic HBV infection ranges from 90% in newborns, 25% to 30% in infants and children under five, and to less than 5% in adults.[31–34] Chronic HBV infection can be classified into five phases: immune tolerant, immune active, inactive chronic infection, chronic disease, and recovery. Each phase of infection has characteristic serologic patterns and correlate with the patient's immune response to HBV.[31,35–37] A good understanding of HBV serologic test results is essential for diagnosis and management (Table 2).

Patients with serologic evidence of resolution, spontaneously or after treatment, show clearance of hepatitis B surface antigen (HBsAg), positive hepatitis B core antibody (HBcAb), and hepatitis B surface antibody (HBsAb). In these patients, the immune system inhibits the replication and gene expression of HBV.

HBV reactivation is defined as the reappearance of active hepatic necroinflammatory disease in a person known to have the inactive HBsAg carrier state or resolved hepatitis B infection.[38–39] It has been reported in 20% to 50% of HBV carriers undergoing immunosuppressive therapy or chemotherapy.[3–6] Clinical manifestations include nonspecific symptoms like fatigue, general malaise, jaundice, hepatic decompensation, fulminant hepatic failure manifested with hepatic encephalopathy, coagulopathy, and even death. Patients can also present with asymptomatic hepatitis flares identified only by biochemical and molecular profiling.

Table 1. American Association for the Study of Liver Disease (AASLD) screening guidelines for HBV and HCV

🚩AASLD screening guidelines for HBV and HCV

HBV

- Individuals born in areas of high or intermediate prevalence rates for HBV, including immigrants and adopted children[a]
- US born persons not vaccinated as infants whose parents were born in regions with high HBV endemicity
- Household and sexual contacts of HBsAg-positive persons
- People who have ever injected drugs
- People with multiple sexual partners or history of sexually transmitted disease
- Men who have sex with men

- Inmates of correctional facilities
- Individuals with chronically elevated ALT or AST
- Individuals infected with HCV or HIV
- Patients undergoing renal dialysis
- All pregnant women
- Persons needing immunosuppressive therapy

HCV

- At least once in people born between 1945–1965
- People who have use injected or intranasal illicit drugsin the recent and remote past, including those who injected only once and do not consider themselves to be drug users
- People with conditions associated with a high prevalence of HCV infection, including people with:
  - · HIV infection
  - · Hemophilia who received clotting factor concentrates prior to 1987
  - · People who have ever been on hemodialysis
  - · People who were incarcerated
  - · People who received tattoos in unregulated settings
  - · Unexplained abnormal aminotransferase levels

- Prior recipients of transfusions or organ transplants prior to July 1992 including persons who:
  - · Were notified that they had received blood from a donor who later tested positive for HCV infection
  - · Received a transfusion of blood or blood products
  - · Received an organ transplant
- Children born to HCV-infected mothers
- Health care, emergency medical and public safety workers after a needle stick injury or mucosal exposure to HCV-positive blood
- Current sexual partners of HCV-infected persons
- Annual testing for people with ongoing risk factors for HCV exposure

[a]Areas of high or intermediate prevalence rate for HBV: Asia, Africa, South Pacific Islands, Middle East (except Cyprus and Israel), European Mediterranean (Malta and Spain), The Arctic (indigenous populations of Alaska, Canada, and Greenland), South America (Ecuador, Guyana, Suriname, Venezuela, and Amazon regions of Bolivia, Brazil, Colombia, and Peru), Eastern Europe (all countries except Hungary), Caribbean (Antigua and Barbuda, Dominica, Granada, Haiti, Jamaica, St. Kitts and Nevis, St. Lucia, and Turks and Caicos), Central America (Guatemala and Honduras).

The timing of reactivation after treatment with biologics is variable. The proposed mechanism of HBV reactivation is divided into three stages.[7,38–40] The initial stage is characterized by viral replication, which is due to the host's decreased immune response. During this stage, serum levels of HBV DNA, HBeAg, and HBsAg are increased, and HBsAb level is decreased. Immunosuppressive agents, such as corticosteroids, may also play a stimulatory role in the production of HBV DNA.

The second stage occurs after the discontinuation of biologics and immune reconstitution. Infected hepatocytes are identified as carrying viral antigens and undergo cytotoxic T cell mediated destruction. During this stage, there is active hepatic necroinflammation with an elevation of the aminotransferases and a potential decrease of HBV DNA.

The third stage is the recovery phase, where there is resolution of the necroinflammation, normalization of the aminotransferases, and decrease of HBV DNA to baseline.

Table 2. Interpretation of HBV serologic test results

Interpretation of HBV serologic test results							
	HBsAg	HBsAb	HBcAb IgM	HBcAb IgG	HBeAg	HBeAb	HBV DNA
Acute	+	−	+	−	+	−	+
Resolved HBV	−	+	−	+	−	+	−
Inactive carrier state	+	−	−	+/−	−	+	−
Chronic HBV	+	−	−	+/−	+/−	−	+
Vaccine induced immunity	−	+	−	−	−	−	−

HBsAg: hepatitis B surface antigen; HBsAb: hepatitis B surface antibody; HBcAb: hepatitis B core antibody; HBeAg: hepatitis b envelope antigen; HBeAb: hepatitis B envelope antibody.

This phase is not observed in patients with fulminant hepatic failure or death. Patients with evidence of acute on chronic liver disease are at higher risk of developing liver failure.[39]

In a systematic review encompassing all studies from 2006–2010, 25 articles with a total of 35 cases of HBV reactivation subsequent to TNF-α inhibitors were identified.[16] All 35 cases were HBsAg positive prior to initiation of the inhibitors. Indications for treatment included rheumatoid arthritis, Crohn's disease, and ankylosing spondylitis. Infliximab was used in 17 cases, etanercept in 12 cases, and adalimumab in six cases. Infliximab was associated with a greater than 2-fold increase in alanine aminotransferase (six of nine cases) and greater than 1,000-fold increase in HBV DNA viral load (three of four cases). Two deaths were reported with the use of infliximab.

Pei *et al*. identified 115 B cell lymphoma patients who received rituximab-containing therapy. HBsAg positivity was found in 15 patients, where five received lamivudine prophylaxis and did not develop HBV-related hepatitis. Eight of 10 patients who were HBsAg positive without lamivudine prophylaxis experienced HBV-related hepatitis, including one fatal hepatic failure. Four (4.2%) of 95 HBsAg negative patients experienced seroconversion and developed *de novo* HBV-related hepatitis, two of which died of fulminant hepatitis.[17]

Rituximab, a chimeric monoclonal antibody against the protein CD20 in B cells, is a major risk factor for the development of HBV reactivation. It causes apoptosis of B cells, therein limiting the immunehost response towards HBV by decreasing antigen presenting cell activity and cytotoxic response of CD8 T lymphocytes.[7,38–40]

Hepatitis B reactivation prevention and treatment

HBV reactivation related morbidity and mortality rates can be reduced by identifying early patients at risk and initiating prophylactic antiviral treatment.[31,40–46] The Asian Pacific Association for the Study of Liver Disease (APASL) recommends that all patients in need of the use of biologics and other immunosuppressive therapy should be screened for HBsAg prior to utilization of treatment (Table 3).[59] The American Association for the Study of Liver Disease (AASLD) and the European Association for the Study of Liver Disease (EASL) recommend performing HBV serologies and liver function tests to diagnose HBV infection.[31,45] If there is evidence of past or present HBV infection, quantitative HBV DNA viral load should be tested, and patients should be referred to a hepatologist for evaluation. Both active and inactive carriers need to start prophylactic antiviral treatment. Following the most recent guidelines issued by the AASLD and EASL, HBsAg positive patients should be treated with lamivudine or telbivudine if the anticipated duration of treatment is less than 12 months and baseline serum HBV DNA is not detectable. Tenofovir or entecavir is preferred if a longer treatment duration is anticipated. Patients with baseline HBV DNA <2,000 IU/mL should continue treatment for 6 months after completion of chemotherapy or immunosuppressive therapy, while patients with higher baseline HBV DNA levels should continue the same treatment strategy as immunocompetent patients.[31,45]

HBsAg-negative patients with positive HBcAb should be tested for HBV DNA. Such patients with detectable serum HBV DNA need to start prophylactic antiviral treatment. However, if HBV DNA is undetectable, current data is insufficient to advocate for the use of prophylactic antiviral treatment. In that case, very close follow up of alanine aminotransferase (ALT) and HBV DNA testing is necessary, and prophylactic antiviral treatment should be initiated if HBV DNA becomes detectable (Fig. 1). EASL guidelines recommend monitoring every 1–3 months, depending on the type of immunosuppressive therapy and comorbidities (Table 4).

Hepatitis C reactivation

Approximately 5.2 million people in the US suffer from chronic HCV infection.[2] Among patients exposed to HCV, up to 85% will become chronically infected, and 5–25% of those cases will develop cirrhosis after 10 years.[47] In contrast to HBV reactivation, HCV reactivation is very uncommon.[7–13] Following immunosuppressive therapy, an increase of viral load to at least one log10 IU/mL above the baseline has been reported.[13,39,48] The clinical manifestations of HCV reactivation may vary from asymptomatic to at least a three-fold increase in aminotransferases. Cases of severe hepatic failure have been reported.[7–13,39,48]

The incidence of hepatic toxicity in HCV infected patients receiving chemotherapy is higher than in patients without HCV infection. Mahale *et al*. reported HCV reactivation in 36% of patients with chronic HCV and cancer.[13] It was difficult to identify the specific chemotherapeutic agents causing hepatotoxicity in the Mahale study, as various agents were utilized. The most commonly used agents preceding HCV reactivation were cytarabine, etoposide, and rituximab. Other reports have been published regarding potential HCV reactivation when utilizing rituximab.[13,25–28]

Aksoy *et al*. reported a case of a patient with history of HCV cirrhosis who presented with a breast lesion due to large B-cell lymphoma.[26] The patient was treated with rituximab monotherapy for three consecutive weeks, but treatment had to be discontinued as a result of hematological toxicity. The HCV viral load was increased three and ten weeks after therapy, but the biochemical profile remained unchanged. After discontinuation of rituximab, the viral load decreased gradually. Tsutsumi *et al*. also reported increases in HCV viral load in four patients receiving rituximab for the treatment of non-Hodgkin's lymphoma.[27] The HCV viral load was elevated after the administration of rituximab or a rituximab containing regimen, and, in one case, viral load was decreased after switching to a treatment without rituximab. The pathogenesis of HCV reactivation following immunosuppressives remains to be elucidated, although an increase in HCV replication as a

Table 3. APASL screening and treatment guidelines for HBV prior to utilization of biologics

| 📌APASL screening and treatment guidelines for HBV prior to utilization of biologics |
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| All candidates for chemotherapy and immunosuppressive therapy should be screened for HBsAg prior to utilization of treatment. |
| If HBsAg (+) patients should start nucleoside/nucleotide analogues if clinically indicated. |
| Start preemptive therapy with lamivudine up to at least 6 months after the end of immunosuppression or chemotherapy. |
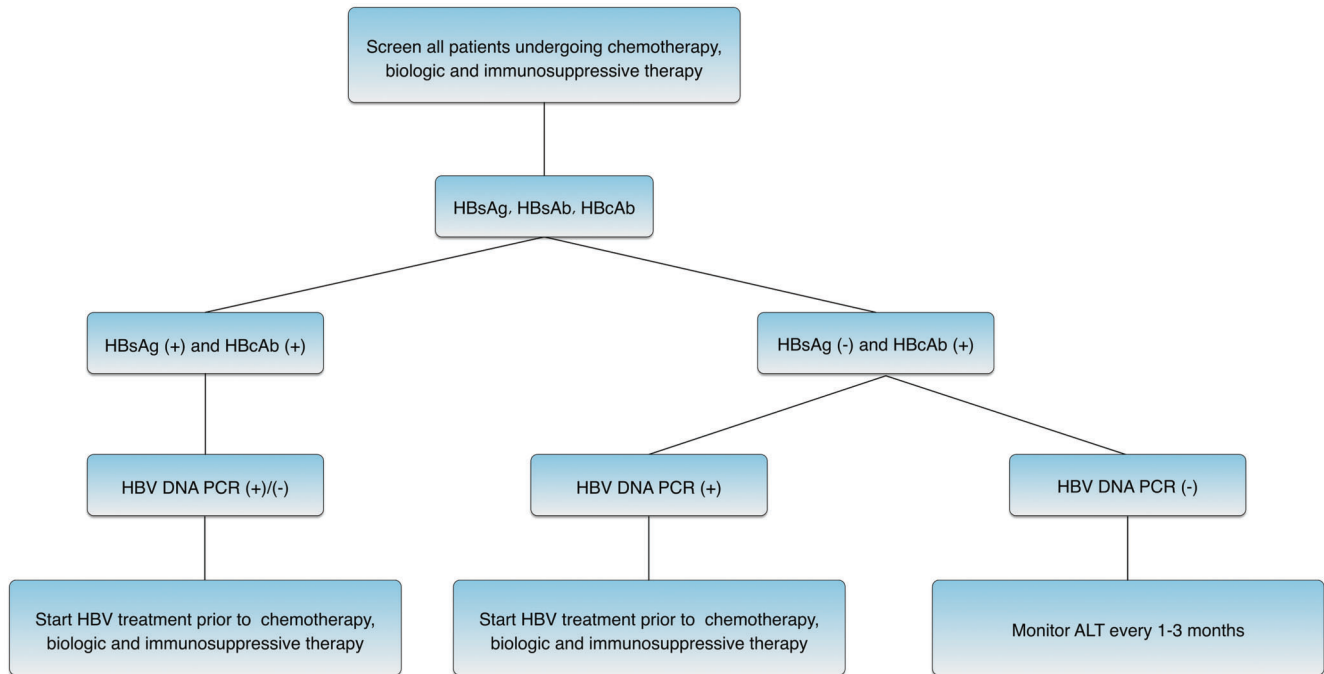
Fig. 1. Algorithm for the management of HBV reactivation. All patients in need of the use of biologics and other immunosuppressive therapy must have HBV serologiesto diagnose HBV infection. HBsAg-positive and HBcAb-negative patients should be treated with lamivudine or telbivudine if the anticipated duration of treatment is less than12 months and baseline serum HBV DNA is not detectable. Tenofovir or entecavir is preferred if longer duration of treatment is anticipated. HBsAg-negative patients with positive HBcAb should be tested for HBV DNA. Such patients with detectable serum HBV DNA need to start prophylactic antiviral treatment. However, if HBV DNA is undetectable, current data is insufficient to advocate for the use prophylactic antiviral treatment. In that case, very close follow up of ALT and HBV DNA testing every 1–3 months is necessary, and prophylactic antiviral treatment should be initiated if HBV DNA becomes detectable.

direct cytopathic effect has been postulated.[10,40] This, followed by the reconstitution of the immune system upon discontinuation of immunosuppressive agents, might lead to direct hepatotoxicity and cell death.

Recurrence of HCV has also been reported in patients after solid organ transplant.[47,49–52] After liver transplant, HCV recurrence is universal and the majority of patients will demonstrate histological evidence within the first year after transplantation. Accelerated progression of fibrosis is seen in 6–23% of patients, who will develop cirrhosis after a median of 3.4 years. The exact mechanism by which this occurs is unknown, although immunosuppressive therapy is thought to play an important role.[47] Similarly, studies performed on various solid organ transplants, including patients with

Table 4. EASL screening and treatment guidelines for HBV and HCV prior to utilization of biologics

EASL screening and treatment guidelines for HBV prior to utilization of biologics
All candidates for chemotherapy and immunosuppressive therapy should be screened for HBsAg and HBcAb prior to utilization of treatment.
Vaccination of HBV seronegative patients is highly recommended.
HBV DNA levels should be tested in HBsAg (+) patients, and preemptive nucleoside/nucleotide analogues started during therapy and for 12 months after cessation of therapy.
Patients with HBV DNA level <2,000 IU/mL should be treated with lamivudine if a short duration with immunosuppressives is expected.
Patients with high HBV DNA level or immunosuppressive therapy of long duration should be treated with entecavir or Tenofovir, which are agents with high antiviral potency and high barrier to resistance.
Patients with HBsAg (−) and HBcAb (+) should have ALT and HBV DNA levels monitored every 1–3 months. These patients should be treated upon confirmation of HBV reactivation.
Some experts recommend prophylaxis with lamivudine in all HBsAg (−) and HBcAb (+) patients who receive rituximab and/or combined regimens for hematological malignancies, if they are HBsAb (−) and/or if close monitoring of HBV DNA level is not guaranteed.
Prophylaxis with nucleoside/nucleotide analogues is also recommended for HBcAb (+) patients receiving bone marrow or stem cell transplantation.

chronic HCV, have reported higher mortality rates due to liver related causes.[47,53]

The evidence regarding HCV infection and the use of a TNF-α antagonist is rather different. In a double-blind, randomized, placebo controlled trial; 50 patients with chronic HCV were randomly assigned to receive interferon alfa-2b and ribavirin with either etanercept or placebo for 24 weeks. The results showed that patients in the etanercept plus standard antiviral therapy group had substantially greater viral suppression than the standard antiviral therapy group, 63% vs. 32%, respectively.[54]

Hepatitis C reactivation prevention and treatment

Despite the fact the rate of HCV reactivation is very low, during or after the use of biologic and other immunosuppressive agents, it still remains a significant cause of morbidity.[55] Optimally, these patients would undergo screening for HCV prior to initiation of treatment. Until more prospective studies demonstrate this relationship, caution should be exercised and careful monitoring is recommended for patients with HCV.

Current treatment for HCV infection is rapidly evolving. In 2011, we experienced the beginning of a new era with the Food and Drug Administration (FDA) approval of a new group of direct acting antiviral agents (DAA), namely telaprevir and boceprevir. Since late 2013, additional DAAs, such as sofosbuvir, simeprevir and ladipasvir, were included in the therapeutic armamentarium against HCV. Sofosbuvir is the prodrug of a nucleotide analogue inhibitor of the HCV nonstructural (NS) 5B ribonucleic acid (RNA)-dependent RNA polymerase.[56–58] Simeprevir is a specific inhibitor of the HCV NS3/4A serine protease.[58] In October 10, 2014, the ledipasvir/sofosbuvir combination therapy of DAAs was approved by the FDA for patients with genotype 1. Currently, the next generation of DAAs, including paritaprevir, ombitasvir, dasabuvir, daclatasvir, and asunaprevir among others, are being evaluated by the FDA and other international agencies. Although the guidelines regarding the utilization of the new DAAs should be reviewed prior to or during the utilization of the chemotherapeutic agents, it might be beneficial to consider testing these patients in order to avoid reactivation of the HCV disease.

Differences between HBV and HCV reactivation

As previously mentioned, HBV reactivation has been reported in 20–50% of HBV carriers undergoing immunosuppressive therapy or chemotherapy.[3–6] In contrast, HCV reactivation is rare, although the morbidity and mortality rates are similar to that of HBV reactivation.[7–13] The high incidence of HBV reactivation has allowed researchers to identify three stages of pathogenesis.[7,38–40] These are characterized by viral replication in response to decreased host immunity, immune reconstitution and active hepatic necroinflammation of infected hepatocytes mediated by cytotoxic T cells, and resolution of necroinflammation.

There are still knowledge gaps in the pathogenesis of HCV reactivation following immunosuppressives, but it is thought to be related to an increase in HCV replication leading to direct hepatotoxicity and cell death.[10,40]

Conclusions

Over the last decade, the utilization of biologics and immunosuppressive agents for the treatment of cancer and autoimmune diseases has increased, accentuating the need for HBV and HCV screening. Data suggest that the risk for HBV and HCV reactivation is increased during and after the use of biologics. Efforts should be directed towards early recognition in order to decrease morbidity and mortality. Active HBV patients and inactive carriers should be carefully monitored, and prophylactic antiviral treatment should be started preemptively.

The possibility of HCV reactivation during the use of biologics and chemotherapeutic agents remains to be determined. There is a significant gap in available information, and this lack of datapoints towards an increased need for prospective studies targeting this population. Until more data become available, caution should be exercised and liver enzymes and the viral load should be monitored closely in vulnerable patients.

Conflict of interest

None

Author contributions

Design of paper, review of the literature, evaluation of papers that should be utilized as references and drafting the paper (LBM); review of references, drafting the paper and performing revisions, review of the paper and final approval (NP).

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