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MINIREVIEWS

Hepatitis B virus reactivation in patients treated with monoclonal antibodies

Silvia De Pauli, Martina Grando, Giovanni Miotti, Marco Zeppieri

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Abstract

Hepatitis B virus (HBV) reactivation poses a significant clinical challenge, especially in patients undergoing immunosuppressive therapies, including monoclonal antibody treatments. This manuscript briefly explores the complex relationship between monoclonal antibody therapy and HBV reactivation, drawing upon current literature and clinical case studies. It delves into the mechanisms underlying this phenomenon, highlighting the importance of risk assessment, monitoring, and prophylactic measures for patients at risk. The manuscript aims to enhance the understanding of HBV reactivation in the context of monoclonal antibody therapy, ultimately facilitating informed clinical decision-making and improved patient care. This paper will also briefly review the definition of HBV activation, assess the risks of reactivation, especially in patients treated with monoclonal antibodies, and consider management for patients with regard to screening, prophylaxis, and treatment. A better understanding of patients at risk can help clinicians provide optimum management to ensure successful patient outcomes and prevent morbidity.

Key Words: Hepatitis B virus; Reactivation; Acute infection; Chronic infection; Monoclonal antibodies

Core Tip: Reactivation of hepatitis B (HBV) induces a rapid and acute increase in viral replication in a patient with chronic HBV infection or prior HBV exposure. There is also an increased risk of HBV reactivation in patients treated with monoclonal antibodies. Organ damage can be due to various mechanisms and risk factors that activate the cascade of inflammatory responses, such as direct infection. It is of clinical importance to diagnose, manage, and treat individuals, especially those at risk. Patient outcomes, success of therapy, prevention of complications, and management of existing comorbidities depend on the correct multidisciplinary management in patients at risk.

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INTRODUCTION

Hepatitis B virus (HBV) infection can lead to acute or chronic infectious disease, particularly the latter when the infection is contracted during childhood. Chronic hepatitis B is estimated to affect 291 million people worldwide, of which almost 80% live in developing countries[1]. When the infection becomes chronic, the virus can remain in the organism in a latent form, thus acting as a reservoir for disease reactivation, which can also occur when there is evidence of recovery of the anti-HBV immune capacity (production of anti-HBs)[2].

When a patient is subjected to immunosuppressive therapy, HBV reactivation may occur. This condition is fairly common and can lead to serious consequences. Various treatments can induce viral reactivation, including oncological chemotherapies, checkpoint inhibitor therapies, stem cell treatments, immunobiological agents such as monoclonal antibodies (mAbs), *etc*[3]. The role of mAbs is fundamental in HBV reactivation.

DEFINITION OF HBV REACTIVATION

HBV reactivation can be considered as sudden and high viral replication in a patient with chronic HBV infection or previous viral exposure[4]. The primary HBV infection can be considered resolved by the presence and development of anti-HBs antibodies. However, as previously mentioned, HBV can remain latent in the body, acting as a reservoir for disease reactivation[2]. HBV reactivation can present with various symptoms. There are mild forms of hepatitis but also severe ones, which can lead to acute liver failure and death.

Following the 2018 American Association for the Study of Liver Diseases guidelines[5], the state of HBV reactivation in hepatitis B surface antigen (HBsAg)-positive and anti-HBc-positive patients can be defined according to the following parameters: (1) At least 2 log (or 100-fold) increase in HBV DNA compared to the baseline level; (2) HBV DNA at least 3 log (or 1000) IU/mL in a patient with previously undetectable HBV DNA; and (3) HBV DNA at least 4 log (or 10000) IU/mL if the baseline level is not available.

For HBsAg-negative and anti-HBc-positive patients, HBV reactivation is defined as detectable HBV DNA or reappearance of HBsAg[5].

RISK OF HBV REACTIVATION

The risk factors for HBV reactivation can be summarized into three general areas: (1) Host factors; (2) virologic factors; and (3) type and degree of immunosuppression[6]. Possible host risk factors include: The male sex, older age, presence of cirrhosis, and the type of disease needing immunosuppressive therapies[7]. Virologic factors include high baseline HBV DNA, HBeAg positivity, and chronic hepatitis B[8]. Referring to the risk factors related to immunosuppressive therapy, these depend above all on the type of underlying pathology and its involvement at a systemic level (*e.g.*, hematologic disease). As already mentioned, a variety of treatments may induce HBV reactivation, such as immunosuppressive and chemotherapies which have the greatest risk of causing HBV reactivation. The American Gastroenterology Association (AGA) categorizes drugs based on their potential to cause HBV reactivation[9].

When the risk of causing HBV reactivation is greater than 10%, the drug can be defined as high risk. Among these drugs, there are B-cell-depleting agents, anthracycline derivatives, moderate-dose corticosteroid therapy (*e.g.*, 10-20 mg prednisone daily), or high-dose corticosteroid therapy (*e.g.*, > 20 mg prednisone daily). Drugs classified as having a moderate risk (between 1 and 10%) of reactivation include tumor necrosis factor (TNF)-α inhibitors, cytokine or integrin inhibitors, and tyrosine kinase inhibitors. Lastly, those considered at low risk of HBV reactivation (less than 1%) include immunosuppressive agents (*e.g.*, azathioprine and methotrexate), and corticosteroid therapy[9].

MONOCLONAL ANTIBODIES AND RISK OF HBV REACTIVATION

In this mini-review, the risk of HBV reactivation in patients treated with mAbs is briefly discussed. In a recent review published in Antibodies[10], there is a warning of adverse liver reactions after the initiation of mAbs. Notably, among the mAbs at high risk of HBV reactivation are anti-CD20 agents; TNF-α inhibitors are instead considered by the authors to be moderate risk. The main results of the current literature are summarized in Table 1.

Anti-CD20 agents (ibritumomab, obinutuzumab, ofatumumab, rituximab)

These drugs are widely used today. Rituximab and ofatumumab are humanized antibodies whose function is to bind to the CD20 receptor present on the surface of B lymphocytes, blocking their response and consequently humoral immunity [11,12]. Historically, rituximab has been the most studied drug in this category. The first work that highlighted the association between this drug and viral reactivation was reported by the FDA MedWatch Database[13] where 118 cases of reactivation were reported to occur between 1997 and 2009. Driven by this evidence, in 2013 the manufacturers of these drugs (rituximab and ofatumumab) were required to add label warnings that highlighted the high risk of possible virus reactivation[12]. These data highlight an interesting aspect: the risk of HBV reactivation linked to depletion of CD20+ B lymphocytes by rituximab highlights how important immunity is in controlling the disease itself[14].

Tumor necrosis factor-α inhibitors (e.g., infliximab, etanercept, adalimumab, certolizumab, and golimumab)

Another highly used category of immunosuppressive drugs is anti-TNF alpha. They are widely used in treating rheumatological diseases such as rheumatoid arthritis and psoriasis, but also gastrointestinal diseases such as inflammatory bowel diseases. However, TNF is a fundamental element in countering HBV infection. Several studies have highlighted how it acts on two fronts: inhibiting virus replication and stimulating T cell immunity. The activated T-cells eliminate infected hepatocytes. Starting from this evidence, various authors have proposed that TNF inhibition through the above-mentioned drugs could lead to a slatentization of the virus, which would replicate, generating disease reactivation[15].

Other mAbs with possible risk of HBV reactivation

Several studies demonstrate that other mAbs are at risk of HBV reactivation. Secukinumab is a fully human monoclonal antibody targeting interleukin-17A and is used for psoriatic disease. A recent retrospective study by Megna *et al*[16] highlights how HBV reactivation is possible in patients undergoing treatment with Secukinumab without prophylaxis. Another multi-center prospective cohort study by Chiu *et al*[17] (63 patients involved with concurrent HBV/hepatitis C virus infection) showed that, without antiviral prophylaxis, 15.2% of HBV patients treated with secukinumab exhibited viral reactivation[17]. Considering the data reported in the literature and the evidence cited above, it appears possible, albeit in very limited cases, that B and C viruses can be reactivated in cases of therapy with these molecules without antiviral prophylaxis[16].

Another drug studied for its relation to cases of HBV reactivation is Ustekinumab. It is a human interleukin-12 (IL-12) and IL-23 antagonist used in adult patients affected by plaque psoriasis, active psoriatic arthritis, and moderate-to-severe active Crohn's disease where other therapies have failed (or in case of patients' intolerance). Several studies have reported cases of HBV reactivation in HBsAg-positive patients treated with ustekinumab[18,19].

SCREENING, PROPHYLAXIS, AND TREATMENT

The current approach, according to the indications of the most recent guidelines, suggests that all patients undergoing treatment with drugs at high and moderate risk of HBV reactivation should be subjected to screening (serum evaluation of HBsAg, anti-HBc, and anti-HBs)[6]. For a more complete screening, blood levels of HBeAg, HBV DNA, and aminotransferase should also be evaluated. According to the main guidelines, treatment must be based on two parameters, the levels of aminotransferase and HBV DNA in the serum (> 2000 IU per milliliter), as well as the severity of the liver disease [5,20].

Treatments with nucleoside analogue drugs such as entecavir or tenofovir are recommended in cases of chronic infection complicated by cirrhosis associated with the presence of HBV DNA in the blood[14]. Lamivudine can also be used in these cases but is burdened by high rates of drug resistance. For this reason, the use of entecavir and tenofovir should be preferred in cases where therapy with lamivudine has already been carried out, and tenofovir is to be preferred to entecavir, as explained by Ekpanyapong *et al*[21].

It is good practice to test all patients before starting immunosuppressive treatments. If serological HBV positivity is found, patients at high reactivation risk should undergo prophylactic treatment with anti-HBV nucleoside analogues. This approach saw the greatest chance of preventing viral reactivation[4]. For example, the American Gastroenterological Association recommends prophylaxis for patients undergoing high-risk and moderate-risk immunosuppressive therapy. This prophylactic treatment should be continued for at least 6 mo after the end of immunosuppressive therapy (12 mo if B-cell-depleting agents were used)[9].

There are currently several prophylaxis protocols studied and available. The most frequently used drugs are lamivudine, entecavir, adefovir, tenofovir disoproxil fumarate, and tenofovir alafenamide. All have demonstrated usefulness in preventing HBV reactivation, but entecavir has demonstrated the greatest efficacy in prophylactic treatment [4].

Future and ongoing research on HBV reactivation must evaluate the complexity of this illness. The risk of HBV reactivation can be associated with immunosuppressive therapy and reactivation. These drugs include those used to treat

Table 1 Current literature

Ref.	Type of study	Conclusions
Baldo *et al*[10], 2022	Review	Warning of adverse liver reactions after the initiation of mAbs. mAbs that are at high risk of HBV reactivation, TNF-α inhibitors are at moderate risk
Evens *et al*[13], 2011	Meta-Analysis	118 cases were reported to the US FDA in which rituximab was associated with HBV reactivation
Dusheiko *et al* [14], 2023	Review	B-cell–depleting therapy with rituximab highlights the contribution of memory B cells to HBV control
Nathan *et al*[15], 2006	Review	TNF inhibits hepatitis viral replication and stimulates HBV-specific T-cell responses to clear the virus from infected hepatocytes. TNF could cause increased expression of hepatitis B viral antigens
Megna *et al*[16], 2022	Prospective cohort study	Highlights the risk of HBV reactivation in patients with latent infection treated with secukinumab without prophylaxis
Chiu *et al*[17], 2018	Multicenter Study	Without antiviral prophylaxis, 7 of 46 (15.2%) patients with HBV exhibited viral reactivation during therapy with secukinumab
Chiu *et al*[18], 2013	Clinical Trial	Among 11 patients positive for hepatitis B surface antigen (HBsAg), two out of the seven (29%) patients who did not receive antiviral prophylaxis exhibited HBV reactivation
Ting *et al*[19], 2018	Prospective cohort study	Among the remaining 54 patients classified as inactive HBV carriers, resolved HBV infection, or isolated anti-HBc positivity, only 3 patients experienced virologic reactivation

HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus; TNF: Tumor necrosis factor; US FDA: United States Food and Drug Administration.

autoimmune illnesses, organ transplants, and specific types of cancer. Research should examine how these treatments impact the host immune system and help latent HBV reactivate. Molecular processes and viral components may also significantly contribute. One of the main areas of research is understanding the molecular processes of HBV reactivation. This entails investigating how the virus endures in the liver and how certain circumstances can cause reactivation.

Innovative studies might concentrate on factors related to viruses, including modifications in viral gene expression, mutations, or adjustments in the viral life cycle that support reactivation. Genetic predisposition and host variables may also be significant. Studies may look at host variables that make people more vulnerable to HBV reactivation. This includes genetic variants that could impact the virus's ability to withstand immunological responses or maintain viral latency. Predicting which individuals are more likely to experience reactivation can be aided by identifying particular host variables. Antiviral prophylaxis, timing of therapies, and monitoring techniques are all part of clinical care and prevention. There is also ongoing research on the creation and assessment of preventive interventions such as immunization and antiviral medications.

CONCLUSION

HBV reactivation is a potentially fatal complication after immunosuppressive biological or targeted therapy. Despite monoclonal antibodies having target specificity, they are not free of adverse effects, including HBV reactivation. Reports from the literature demonstrate that this is more frequent in patients treated with anti-CD20 or anti-TNF. However, there are some case reports of other mAbs causing this adverse event. Many unanswered questions remain about the risk of HBV reactivation associated with recently introduced mAbs. These questions provide an opportunity for monitoring and research.

FOOTNOTES

Co-first authors: Silvia De Pauli and Martina Grando.

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