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Reactivation of hepatitis B virus infection after cytotoxic chemotherapy or immunosuppressive therapy

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Abstract

Reactivation of hepatitis B is defined as the recurrence or an abrupt rise in hepatitis B virus (HBV) replication, often accompanied by an increase in serum transaminase levels, and both events occurring in a patient with a previous inactive hepatitis B infection. This reactivation can occur in situations in which the ratio of HBV replication and immune response is altered. It can happen during the treatment of hemato-oncological malignancies with chemotherapy and in immunosuppression of autoimmune diseases. Clinical manifestations of hepatitis B reactivation are variable and can range from asymptomatic to acute hepatitis, which are sometimes serious and result in acute liver failure with risk of death, and usually occur in the periods between cycles or at the end of chemotherapy. Immunosuppressive drugs such as corticosteroids or azathioprine can induce HBV reactivation in patients carrying hepatitis B virus surface antigen (HBsAg) or anti-HBc, but much less frequently than chemotherapy treatments. The tumor necrosis factor α inhibitors infliximab, etanercept and adalimumab may cause reactivation of hepatitis B, and the overall frequency with infliximab may be similar (50%-66%) to that caused by chemotherapy. Baseline HBV serology is recommended for all patients receiving chemotherapy and immunosuppressive drugs, and HBsAg positive patients should receive anti-HBV prophylaxis to decrease virus reactivation and death rates.

Key words: Hepatitis B; Immune response; Immunosuppression; Reactivation

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SITUATIONS ASSOCIATED WITH REACTIVATION OF HEPATITIS B

Hepatitis B is a major health problem worldwide with a prevalence that varies according to geographic area. This prevalence is changing due to the growing phenomenon of immigration. There are four distinct dynamic phases of chronic infection with hepatitis B virus (HBV) and this process is unidirectional, depending on the interaction between the virus itself, hepatocytes and the host immune system[1]. Because of this interaction, situations that lead to immunosuppression in patients with chronic HBV infection may alter the natural history of this infection and give rise to the phenomenon of reactivation.

Reactivation of hepatitis B (HBV reactivation) is defined as the recurrence or abrupt rise in HBV replication by at least an increase in serum HBV DNA levels of 1 $\log_{10}$, often accompanied by an increase in transaminase levels (at least three times the baseline). Both events occur in a patient with a previous inactive HBV infection, i.e. either an inactive carrier state or a patient with resolved hepatitis[2]. HBV reactivation can occur in situations in which HBV replication increases or the immune response decreases. This can happen spontaneously, generally when the virus mutates and the immune system needs time to rebuild the immune response. It also appears when the virus replicates again abruptly and becomes resistant to a drug or when antiviral medications have been withdrawn. In patients with coinfection by the human immunodeficiency virus (HIV) this happens when progressive immunodeficiency lowers specific T cells response against HBV. A major cause of HBV reactivation is solid organ transplantation. Finally, the most common causes and the focus of this report, are chemotherapy (CMT), used in the treatment of onco-hematological diseases, and immunosuppressive drugs used in the treatment of autoimmune diseases (Table 1)[2]. The risk of HBV reactivation depends on factors such as the state of HBV: the higher the level of viral replication, the higher the risk of reactivation. This risk is much lower in patients with resolved infection. Another factor that influences HBV reactivation is the type of disease: the risk is higher in patients with lymphoma than in those with solid tumors. This can be attributed to the fact that hematological disease itself induces a greater degree of immunosuppression or that CMT is stronger in cases of hematological malignancies[3]. All types of drugs used in CMT have been involved in HBV

Table 1 Onco-hematological diseases and reactivation of hepatitis B

Hematologic diseases	Hematological tumors
Non-hodgkin lymphoma	Breast cancer
Hodgkin lymphoma	Lung cancer
Chronic lymphocytic leukemia	Hepatocellular carcinoma
Chronic myeloid leukemia	Nasopharyngeal cancer
Acute myeloid leukemia	Other cancers
Acute lymphoblastic leukemia	
Multiple myeloma	
Waldenstrom macroglobulinemia	
Plasmacytoma	
Aplastic anemia	
Myelodysplastic syndrome	
Bone marrow transplantation	

Table 2 Chemotherapy and reactivation of hepatitis B

Classes	Drugs
Alkylating agents	Cyclophosphamide, chlorambucil, cisplatin
Alkaloids	Vincristine, vinblastine
Antibiotics	Doxorubicin, epirubicin, daunorubicin, bleomycin, mitomycin C, actinomycin D
Antimetabolites	Cytarabine, fluorouracil, gemcitabine, mercaptopurine, methotrexate, thioguanine
Monoclonal antibodies	Rituximab (anti-CD20), alemtuzumab (anti-CD52)
Corticosteroids	Dexamethasone, methylprednisolone, prednisone
Others	Folinic acid, colaspase, docetaxel, etoposide, fludarabine, interferon, procarbazine

with resolved hepatitis, HBV reactivation usually begins later than 4 mo, but has the same clinical features. Sometimes reactivation only occurs with HBV-DNA elevation, without increased transaminases. Other times the patient does not move into the full recovery phase, but has elevated HBV DNA levels, although there is no significant immune reconstitution or liver damage. This is common in patients undergoing organ transplantation and treatment with immunosuppressive drugs. Finally in some cases, the hepatitis phase persists and a chronic hepatitis is established[10].

TREATMENT AND PREVENTION OF HEPATITIS B REACTIVATION

The first step following HBV reactivation is to suspend CMT. However, this can affect the efficacy of this treatment.

Interferon-α is the classic treatment of chronic hepatitis B, but should not be used in cases of HBV reactivation, because its immunomodulatory action can cause a serious hepatitis outbreak that added to HBV reactivation can have serious consequences.

Lamivudine is the most frequently used nucleoside analog in the treatment of HBV reactivation and has been available since 1999. This drug is capable of inhibiting HBV replication and can reverse HBV reactivation. However, treatment with lamivudine can cause mortality in patients with HBV reactivation, which ranges between 13% and 80% with an average of about 36%[2]. Therefore, at least one third of patients die from HBV reactivation despite treatment with lamivudine. This could be due to its lower antiviral potency (less than that of other nucleoside/nucleotide analogs such as telbivudine, entecavir and tenofovir), its high rate of resistance (up to 67% at 4 years in immunocompetent individuals), and possibly because HBV reactivation is less effective when it is already in progress. These facts led to the conclusion that in such patients it would probably be best to administer preventive treatment for HBV reactivation with the aim of inhibiting the replication of HBV, as this would hinder the development of hepatitis and thus mortality.

Prophylaxis in patients treated with chemotherapy

In eight retrospective case studies of patients with positive HBsAg treated with CMT, HBV reactivation occurred in 2.4% of those receiving prophylaxis with lamivudine compared with 56% who did not receive prophylaxis. Similarly, in four prospective case studies with historical controls, HBV reactivation occurred in 4% of those receiving prophylaxis with lamivudine compared with 28% who did not receive prophylaxis[8]. In a prospective controlled clinical trial, prophylaxis with lamivudine for 2 wk before starting CMT and for six wk thereafter was compared to treatment with lamivudine when there was already HBV reactivation. HBV reactivation occurred in 53% of patients who received no prophylaxis, however, none of those who received prophylaxis showed evidence of HBV reactivation; hepatitis occurred in 47% of those without prophylaxis and 7% died. None of the patients who received prophylaxis developed hepatitis or died[11]. A similar trial also compared lamivudine prophylaxis 2 wk prior to CMT until 2 mo after CMT with lamivudine treatment for HBV reactivation. Again there were significant differences in favor of prophylaxis, although this did not prevent reactivation in 12% of cases and hepatitis in 8%, attributable to the average antiviral potency of lamivudine and the possibility of the development of resistance. Importantly, following discontinuation of prophylaxis an increase in the number of patients with hepatitis reactivation, including death, occurred indicating that prophylaxis should be maintained beyond 2 mo after completion of CMT[12]. In another study, prophylaxis was continued for 3 mo after CMT. After 26 mo of follow-up, hepatitis B was reactivated in 24% of patients, and reached 40% at 40 mo, being more common in those patients with high HBV replication at baseline[13]. A meta-analysis of 14 studies also found significant differences in favor of prophylaxis with lamivudine compared with untreated controls, although again prophylaxis with lamivudine did not eliminate all risk of HBV reactivation[5]. Finally, in another systematic review with a meta-analysis that included 21 studies, significantly lower numbers of reactivation, hepatitis and death were found in the group receiving prophylaxis with lamivudine[14]. In summary, the

findings from these 8 retrospective case series, 4 prospective case series with historical controls, two controlled trials published to date and 2 meta-analyses showed that prophylactic lamivudine significantly reduces HBV reactivation. In addition, prophylaxis should last approximately 3 mo after completion of CMT, especially in patients with high HBV replication at baseline. There are no studies on the time prophylaxis should be extended and recommendations by experts range from 6-12 mo post-CMT treatment. These recommendations have even been extended to patients with risk factors such as high basal HBV-DNA, use of rituximab or BMT. All consensus and clinical practice guidelines[15-17] recommend baseline screening for HBV (HBsAg, anti-HBc and anti-HBs) in all patients who are scheduled to receive CMT. In seronegative patients, the possibility of anti-HBV vaccination should be assessed. HBsAg positive patients should receive anti-HBV prophylaxis: patients who undergo CMT for less than 1 year may be treated with lamivudine (100 mg/d) from 1-2 wk before and 6-12 mo after. If CMT continues over 1 year and, especially, if there is high HBV replication, more potent drugs with less resistance such as telbivudine, tenofovir or entecavir should be evaluated. Patients with resolved hepatitis may be carriers of hidden HBV. Thus, HBV reactivation prophylaxis in patients assessed for BMT or subjected to aggressive and prolonged immunosuppressive therapy, such as patients undergoing solid organ transplantation should be considered[4]. The appearance of HBsAg and HBV DNA in up to 50% of patients with anti-HBc undergoing BMT have been reported. The serial determination of anti-HBs in the serum of these bone marrow recipients has shown a steady decline to undetectable levels by 1-3 years after transplantation. With the loss of anti-HBs (anti-HBc), HBV DNA increases and HBsAg reappears. Some of these patients with HBs seroreversion do not develop clinical hepatitis, but among those who have HBs seroreversion, severe infection is rare. HBsAg seroreversion occurs late in patients with BMT, and therefore, in these cases long-term antiviral prophylaxis is recommended[18,19]. Resolved hepatitis B patients with hematologic malignancies who receive CMT may also develop HBV reactivation, especially those with only positive anti-HBc (HBV reactivation in 25%). Risk factors are: negative anti-HBs or serum HBV DNA levels often < 100 IU/mL, treatment with more than one chemotherapeutic agent or with rituximab and BMT. In 20%-40% of cases, HBV reactivation may be fatal and prophylaxis with lamivudine again does not prevent reactivation in all cases[20,21].

Prophylaxis in patients receiving biological treatments

Classical immunosuppressive drugs (corticosteroids, azathioprine, methotrexate) have been used for many years in multiple autoimmune diseases and organ transplantation. These drugs can induce HBV reactivation in patients carrying HBsAg or anti-HBc, but much less frequently than CMT. Therefore, reported cases of HBV reactivation are isolated[2].

Table 3 Infliximab treatment and cases of hepatitis B reactivation

17 reports (2003-2009) (n = 21)	n
Michel *et al*[26], 2003	1
Ostuni *et al*[27], 2003	1
Oniankitan *et al*[28], 2004	1
Esteve *et al*[29], 2004	3
Wendling *et al*[30], 2005	1
Ueno *et al*[31], 2005	1
Anelli *et al*[32], 2005	1
Millonig *et al*[33], 2006	1
Roux *et al*[34], 2006	1
Calabrese *et al*[35], 2006	1
Colbert *et al*[36], 2007	1
Madonia *et al*[37], 2007	1
Sakellariou *et al*[38], 2007	2
Ojiro *et al*[39], 2008	1
Chung *et al*[40], 2009	1
Conde-Taboada *et al*[41], 2009	1
Wendling *et al*[42], 2009	1

The new immunosuppressants are called biological therapies, because these drugs block the action of biological products involved in the immune-inflammatory pathogenesis of many diseases. There are four main types: anti-inflammatory cytokines, anti-lymphocyte, anti-leukocyte adhesion and migration and anti-immunoglobulin[22]. Within the first group of anti-cytokines there are tumor necrosis factor (TNF)α inhibitors, such as infliximab, etanercept and adalimumab. All three are used in the treatment of various rheumatic diseases and inflammatory bowel disease[23], since the cytokine TNFα is dominant in these diseases and its inhibition improves the disease. However, the inhibition of TNFα can reactivate hepatitis B[24], as TNFα is also important in the immune pathogenesis of hepatitis B, it takes part in cytolytic immunodepletion by CD8 cytotoxic lymphocytes, and is involved in noncytolytic immunodepletion with other cytokines produced by CD4 lymphocytes suppressing HBV replication and, ultimately, increases all immunocompetent cells. Therefore, administration of anti-TNFα inhibits the anti-HBV immune response, thus favoring HBV replication and the expression of a large amount of hepatitis B virus core antigen (HBcAg) in infected hepatocytes. When the administration of anti-TNFα is suspended, inhibition of the immune response is stopped and thus, there is immune reconstitution which attacks the large number of hepatocytes expressing HBcAg in their membranes. This results in an outbreak of hepatitis[25].

Seventeen publications in the past 6 years have reported 21 patients who experienced reactivation of hepatitis B when treated with infliximab (Table 3). Infliximab was used to treat Crohn's disease in 8 cases, rheumatoid arthritis in 6 patients, ankylosing spondylitis in 5 cases, Still's disease in 1 case and psoriasis in 1 case. HBV infection at baseline was the inactive carrier state in 15 cases, chronic active hepatitis in 4 cases, occult HBV in 1 case and delta virus co-infection in 1 case. None of the six

patients who received lamivudine prophylaxis had HBV reactivation. This was not the case in the remaining 15 patients who did not receive prophylaxis and were distributed as follows: in 8 cases (53%), reactivation was treated with lamivudine and the outcome was good, 3 cases (20%) had fatal fulminant hepatitis, in another 3 cases (20%) withdrawal of infliximab was followed by regression of the alterations, and in one case (7%) evolution was spontaneously favorable. It should be noted that the usual pattern of treatment with infliximab in these publications was three doses at week 0, 2 and 6 followed by maintenance treatment every 8 wk. It is, therefore, a long-term treatment and resistance to lamivudine can appear, particularly in patients with high HBV replication. In such cases, it is preferable to use drugs with lower rates of resistance such as tenofovir or entecavir.

In the last 3 years, 7 patients who had HBV reactivation with etanercept have been reported. All had rheumatic disease and 5 patients at baseline were in the inactive carrier state of HBV, one patient had chronic active hepatitis and the other case had hidden hepatitis B infection. None of the three patients receiving prophylaxis with lamivudine showed reactivation of hepatitis B. Of the four patients without prophylaxis, 3 responded favorably to treatment with lamivudine and 1 responded without treatment. These results suggest that etanercept could lead to a revival milder than that with infliximab, but it is difficult to determine because it was described as a case of reactivation of resolved hepatitis, which generally is interpreted as a result of increased immunosuppression[43].

To our knowledge, there are only two case reports of HBsAg-positive patients treated with adalimumab, which accounted for three patients with rheumatoid arthritis and an inactive carrier state of HBV[44,45]. In one case, lamivudine prophylaxis was administered and there was no HBV reactivation. Of the other two cases, one had an increase in HBV DNA, which remained stable for 2 years without associated hepatitis, despite continuing with adalimumab; the other case did not show any evidence of reactivation. It is difficult to draw conclusions from so few data, except to say that prophylaxis prevents HBV reactivation.

Both etanercept and adalimumab probably cause less HBV reactivation than infliximab. In a series of 103 patients with rheumatic diseases treated with anti-TNFα, 8 cases were inactive HBsAg carriers and 2 cases were treated with infliximab, 4 cases with etanercept and 2 cases with adalimimab HBV reactivation occurred in one of these 8 patients and this patient was one of the two treated with infliximab[46]. Thus, the frequency of reactivation with infliximab may be 50%, similar to that observed with cancer treatments. However, there is evidence that this frequency may be even higher. In another series of 80 cases of Crohn's disease treated with infliximab, 3 patients were HBsAg positive: one of them received prophylaxis with lamivudine and demonstrated no evidence of HBV reactivation, but the other two cases who received no prophylaxis demonstrated evidence of HBV reactivation, i.e. the frequency of HBV reactivation was 66%[47].

CONCLUSION

In HBsAg carriers who undergo CMT, the risk of HBV reactivation is high: 30%-50%. The risk is greater in patients with high HBV replication at baseline, and in patients receiving CMT regimens which include corticosteroids or rituximab, or individuals who undergo a BMT. These patients should be screened for HBV at baseline: HBsAg, anti-HBc and anti-HBs. Anti-HBV vaccination should be assessed for seronegative patients.

Anti-HBV prophylaxis is indicated in patients with positive HBsAg, to decrease reactivation rates, hepatitis and death. Although there is a lack of information, prophylaxis should begin 1-2 wk prior to CMT and should be maintained until 6-12 mo after treatment. A longer treatment period may be necessary in patients with factors that promote reactivation.

Most studies on prophylaxis have been conducted with lamivudine. This drug should be used in patients with low HBV DNA levels at baseline who will receive treatment for less than 1 year. In other cases, more potent drugs with less risk of resistance such as tenofovir or entecavir should be used.

Positive anti-HBc patients may have an occult HBV infection that can be reactivated by CMT. There is insufficient evidence to recommend routine prophylaxis, but treatment is recommended for patients with risk factors and, in other cases, follow-up and early treatment should be recommended in case of reactivation.

The TNFα inhibitors infliximab, etanercept and adalimumab may cause reactivation of HBV. The overall frequency seems less than that caused by CMT, but the frequency with infliximab may be similar (50%-66%). Prophylaxis prevents HBV reactivation in patients treated with infliximab. There are insufficient data to advise routine prophylaxis with etanercept and adalimumab, but until such data are available it seems prudent to administer prophylaxis.

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