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## Hepatitis B and inflammatory bowel disease: Role of antiviral prophylaxis

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antigen should receive antiviral prophylaxis before undergoing immunosuppression in order to avoid HBV reactivation. Tenofovir/entecavir are preferred to lamivudine as nucleos(t)ide analogues due to their better resistance profile. In patients with occult or resolved HBV, viral reactivation does not appear to be a relevant issue and regular DNA determination is recommended during immunosuppression therapy. Consensus guidelines on this topic have been published in recent years. The prevention and management of HBV infection in IBD patients is addressed in this review in order to address practical recommendations

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**Key words:** Hepatitis B virus; Inflammatory bowel disease; Anti-tumor necrosis factor; Prophylaxis; Immunosuppressants

### Abstract

Hepatitis B virus (HBV) is a very common infection worldwide. Its reactivation in patients receiving immunosuppression has been widely described as being associated with significant morbidity and mortality unless anti-viral prophylaxis is administered. Treatment in inflammatory bowel disease (IBD) patients has changed in recent years and immunosuppression and biological therapies are now used more frequently than before. Although current studies have reported an incidence of hepatitis B in inflammatory bowel disease patients similar to that in the general population, associated liver damage remains an important concern in this setting. Liver dysfunction may manifest in several ways, from a subtle change in serum aminotransferase levels to fulminant liver failure and death. Patients undergoing double immunosuppression are at a higher risk, and reactivation usually occurs after more than one year of treatment. As preventive measures, all IBD patients should be screened for HBV markers at diagnosis and those who are positive for the hepatitis B surface

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### INTRODUCTION

Approximately 3 billion people have been exposed to the hepatitis B virus (HBV), and there are an estimated 350 million chronic carriers worldwide<sup>[1,2]</sup>. Exposure to HBV can be broadly divided into three categories according to viral load and liver biopsy<sup>[1,3]</sup>: active HBV, inactive HBV carriers and resolved HBV (Table 1). Chronic hepatitis B (CHB) may result in cirrhosis in about 5%-25% of infected patients.

Active chronic HBV is defined as HBV DNA levels  $\geq 2$  IU/L and elevated alanine aminotransferase (ALT) levels, and treatment is indicated in either immunocom-

petent or immunosuppressed patients.

Inactive hepatitis B is defined by HBV DNA levels  $\leq 2$  IU/L and normal ALT levels, and antiviral therapy is not indicated in immunocompetent patients. However, in patients treated with immunosuppressant drugs, viral reactivation may occur regardless of DNA levels, so antiviral prophylaxis must be established.

Finally, patients with resolved HBV infection do not need antiviral therapy, but they must be monitored during immunosuppressant therapy and considered for prophylactic therapy based on the progression of anti-HBc or HBV DNA levels.

Ulcerative colitis (UC) and Crohn's disease (CD) are chronic inflammatory conditions of the gastrointestinal tract. In the last 10 years, treatment of these inflammatory bowel diseases (IBD) has been markedly changed by the use of immunosuppressants (mainly azathioprine/mercaptopurine and methotrexate) and biological therapies. There is an increasing trend towards earlier and more extensive use of these drugs for longer periods of time. As a result, concerns regarding safety related to immunosuppressive treatment are growing<sup>[4,5]</sup> among the professionals involved in providing IBD care. One of these issues is related to the reactivation of hepatitis B; immunomodulator therapy has a clear impact on the natural history of viral hepatitis and there are many unresolved questions concerning the relationship between IBD and HBV that must be resolved. The management of IBD patients with viral hepatitis B is addressed in this review.

## PREVALENCE OF HBV INFECTION IN IBD PATIENTS

The first step in addressing the problem is to identify its impact. The prevalence of patients with IBD who are at risk for hepatitis B reactivation has been clarified in a prospective cross-sectional nationwide study in Spain<sup>[6]</sup>. In this multicentre study of 2076 IBD patients, the prevalence of biological markers of present and/or past hepatitis B was lower than reported in previous studies and similar to the Spanish general population: less than 1% of IBD patients had positive hepatitis B surface antigen (HBsAg) and less than 10% had positive hepatitis B core antibody (HBcAb), without differences between CD and UC patients (7.1% and 8% respectively). Similar results were also shown in a recent study in France<sup>[7]</sup>, where HBcAb was reported in only 2.78% and 1.59% of CD and UC patients, respectively; similar rates were observed in the general French population.

In previous studies<sup>[8-10]</sup>, the prevalence of HBV infection in IBD patients was shown to be comparatively higher. Biancone *et al*<sup>[9]</sup> reported positive anti-HBc in 10.9% and 11.5% of CD and UC patients in Italy, respectively, compared to 5.1% in controls ( $P < 0.02$ ). The risk of viral hepatitis in IBD patients has been associated with blood transfusions and surgery<sup>[11,12]</sup>, suggesting nosocomial transmission of the virus. The decreasing prevalence

of viral hepatitis in IBD patients in current reports from Spain and France suggests that preventative measures such as vaccination, the World Health Organization blood transfusion safety programs, single-use materials, and better aseptic perioperative rules and decontamination procedures in endoscopy<sup>[7]</sup>, have been effective and explains the diminishing risk for HBV.

## EFFECT OF IMMUNOSUPPRESSIVE THERAPY ON HBV INFECTION

Reactivation of HBV infection is a well-described complication of immunosuppression in the setting of organ transplantation or cancer chemotherapy<sup>[13]</sup>. The frequency of HBV reactivation depends on the type of immunosuppression and the state of HBV infection when chemotherapy is administered<sup>[14-16]</sup>. Cytotoxic chemotherapy for hematologic malignancies appears to involve the greatest risk of HBV reactivation; spontaneous reactivation may occur in up to 22% of inactive HBV carriers, but this may increase up to 60% of patients in the case of cytotoxic chemotherapy for lymphoma, with a mortality rate between 4% and 60% if fulminant liver failure occurs<sup>[17-19]</sup>.

In patients undergoing treatment with biologic agents, hepatitis B reactivation represents an emerging cause of liver disease<sup>[20]</sup>. In particular, the risk of HBV reactivation is greatly increased with the use of monoclonal antibodies such as rituximab (anti-CD20) and alemtuzumab (anti-CD52)<sup>[21-23]</sup>. Based on the liver damage that occurs after viral reactivation, three kinds of liver disease<sup>[4]</sup> can be distinguished: viral reactivation or replication, acute liver failure, and fulminant liver failure. For hepatitis B, reactivation is defined as a 1.5-2-fold increase in ALT compared with the baseline value plus an increase in HBV DNA levels  $> 2$  IU/L or DNA reappearance in a previously negative patient<sup>[24,25]</sup>. Acute liver failure is defined as sudden and severe impairment of liver function (bilirubin  $> 2$  mg/dL, albumin  $< 34$  g/L or prothrombin time  $< 50\%$ ), meanwhile fulminant liver failure is a severe acute failure complicated by hepatic encephalopathy, liver transplantation, or death<sup>[25]</sup>.

Fatal viral reactivation has also been described in patients with IBD or other autoimmune diseases treated with immunosuppressant drugs<sup>[26-29]</sup>. Tumor necrosis factor alpha (TNF- $\alpha$ ) is important in regulating hepatitis B replication<sup>[30]</sup>, and the chimeric anti-tumour necrosis factor alpha monoclonal antibody infliximab has been involved in hepatitis B reactivation following treatment<sup>[31-35]</sup>. However, the factors that may increase the risk are not properly defined<sup>[36,37]</sup>. Additionally, there are no specific data on prophylaxis in IBD patients, the type and the timing of treatment, and which individuals make the most suitable candidates<sup>[38-40]</sup>.

Most of the information available comes from case reports about HBV reactivation in patients with CD or UC, both after the use of corticoids, with or without azathioprine and biologic therapy with infliximab<sup>[41]</sup>.

**Table 1** Definitions of hepatitis B virus infection

	HBsAg	HBsAb	HBcAb	HBV DNA		ALT/AST	Liver biopsy
				HBeAg (+)	HBeAg (-)		
Chronic HBV	Positive	Negative	Positive	> 20000 IU/mL	> 2000 IU/mL	Elevated	Chronic hepatitis with necroinflammation
Inactive HBV Carrier	Positive	Negative	Positive	< 20000 IU/mL	< 2000 IU/mL	Normal	No significant hepatitis
Resolved HBV	Negative	Positive	Positive	Undetectable	Undetectable	Normal	No significant hepatitis

HBV: Hepatitis B virus; HBsAg: Hepatitis B surface antigen; HBsAb: Hepatitis B surface antibody; HBcAb: Hepatitis B core antibody; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase.

In 2004, Esteve *et al*<sup>[42]</sup> reported three CD patients, which were hepatitis B carriers, treated with infliximab. One of them received concomitant lamivudine therapy and experienced no variations in clinical or biochemical liver parameters. However, the other two patients suffered from viral reactivation; one patient died and the other resolved after specific treatment. Reactivation may occur as soon as after the first infusion or as late as 2 years after starting infliximab, indicating that it may develop at any time during anti-TNF therapy, however, the time between the start of TNF- $\alpha$  inhibitors and the occurrence of hepatitis is usually longer than one year<sup>[43]</sup>.

A relevant characteristic is that almost all cases of infliximab-associated HBV reactivation have occurred in patients receiving concomitant treatment with other immunosuppressants such as corticosteroids or thiopurines, suggesting that more profound immunosuppression may facilitate viral reactivation<sup>[26,38-40]</sup>. In a Spanish cooperative study (REPENTINA-2) on this problem<sup>[26]</sup>, 120 patients with hepatitis B or hepatitis B and C markers who had been treated with immunosuppressive therapy during a median time of 1 year were identified. The authors retrospectively assessed the frequency and severity of liver disease in these patients based on exposure to one or more immunosuppressive drugs. Although they identified 25 HBsAg-positive patients, unfortunately only 6 of them had received antiviral treatment before immunosuppression. Nine of these 25 patients developed liver disease, six developed liver failure, and none had fulminant liver failure. Almost all cases of HBV reactivation associated with infliximab occurred in patients receiving concomitant treatment with other immunosuppressants. REPENTINA-2 also showed that no single immunosuppressant seems to be specifically involved in the development of liver failure, and the risk of hepatitis B reactivation seems to be related to the magnitude of immunosuppression.

Regarding other anti-TNF treatments, reactivation has also been reported with adalimumab or etanercept in patients with rheumatoid arthritis<sup>[44-46]</sup>, but not from IBD patients or those taking certolizumab pegol. As these are newer TNF antagonists, the risk of hepatitis B reactivation is expected to be similar due to a class effect<sup>[4,15]</sup>.

Regarding patients with resolved HBV infection, reactivation following chemotherapy has also been reported in up to 40% of patients<sup>[17,47-49]</sup>, though the risk in IBD seems to be much lower. Although there has been a

report of reactivation after treatment with infliximab in a patient with CD and occult HBV infection<sup>[47]</sup>, no cases were described in the REPENTINA-2 study. In other autoimmune diseases such as rheumatoid arthritis (RA), this issue has also been examined and reactivation rates have not been relevant<sup>[50,51]</sup>. Tamori *et al*<sup>[52]</sup> followed 50 patients with RA who were positive for HBcAb for a mean period of 23 mo. All were patients treated with immunosuppressive agents such as methotrexate, prednisolone, and/or TNF- $\alpha$  inhibitors for more than one year. HBV reactivation was observed in two out of five patients with HBsAg, compared with only one of the remaining 45 patients without it.

On the other hand, the results from a retrospective analysis of 62 psoriatic patients<sup>[53]</sup> with occult HBV infection, treated with anti-TNF biological agents, and without signs of HBV activation after a period of 4 years, also suggest the overall safety of treatment with anti-TNF and/or immunosuppressants drugs in HBV occult carriers.

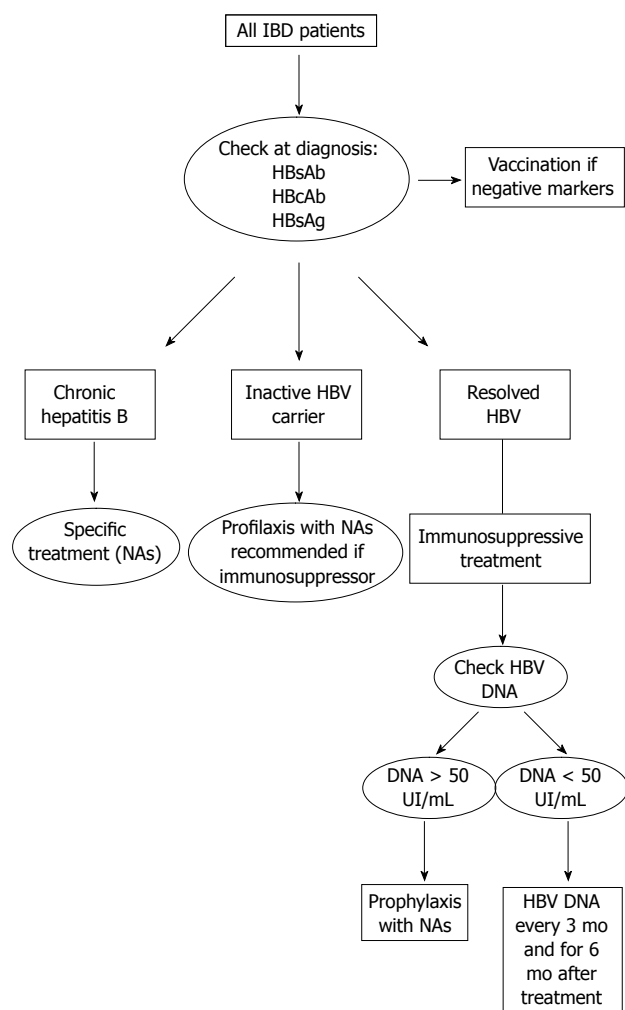
## SCREENING RECOMMENDATIONS

Screening measures must be instituted in IBD patients<sup>[4,54-56]</sup>. Recommendations are based on the potentially fatal consequences of HBV reactivation, as we have seen previously, and the availability of safe and effective anti-HBV drugs to prevent them<sup>[57]</sup>. Current guidelines by the American Association for the Study of Liver Diseases (AASLD) recommend HBV screening for populations with an intermediate or high prevalence ( $> 2\%$ ) and those requiring immunosuppression, including IBD patients<sup>[3]</sup>.

Screening for HBV should be performed at the time of IBD diagnosis rather than delaying until consideration of immunomodulators or TNF antagonist medication<sup>[3,58-60]</sup>. The hepatitis B surface antibody (HBsAb), and the HBsAg and HBcAb are recommended as screening tests. Although the utility of HBcAb is controversial, it may represent chronic HBV despite undetectable HBsAg/HBsAb in immunosuppressed patients or those co-infected with hepatitis C or human immunodeficiency virus<sup>[3,58]</sup>, but it may also be falsely elevated in a low percentage of patients.

## ANTIVIRAL PROPHYLAXIS

In accordance with specific guidelines for hepatitis B



**Figure 1** An algorithm for the management of patient with inflammatory bowel disease with different hepatitis B virus infection status. NAs: Nucleos(t)ide analogues; IBD: Inflammatory bowel disease; HBV: Hepatitis B virus; HBsAg: Hepatitis B surface antigen; HBsAb: Hepatitis B surface antibody; HBcAb: Hepatitis B core antibody.

(Figure 1)<sup>[3]</sup>, patients with high baseline HBV DNA levels (> 2 IU/L) should continue antiviral treatment until the endpoints applicable to non-immunosuppressed patients are reached.

Prophylaxis must be considered in patients with HBsAg without active viral replication prior to undergoing treatment with any immunosuppressant medication, including steroids, immunomodulators or biologicals, in order to prevent reactivation<sup>[3,59]</sup>.

While there are no data specifically for IBD, recommendations are extrapolated from randomized controlled trials in patients undergoing chemotherapy<sup>[60-62]</sup> in which prophylaxis has been shown to be beneficial<sup>[63,64]</sup>. Lau *et al.*<sup>[65]</sup> randomized 30 lymphoma patients with HBV markers to lamivudine prophylaxis or no prophylaxis before chemotherapy. None of the patients receiving prophylaxis developed HBV reactivation, compared to 53% of those in the no prophylaxis group ( $P = 0.002$ ). A recent meta-analysis<sup>[66]</sup> of lamivudine in immunosuppressed patients included 21 studies and showed a mortality benefit

for lamivudine (OR: 0.36; 95%CI: 0.23-0.56).

The AASLD<sup>[3]</sup> and the European Association for the Study of the Liver<sup>[67]</sup> recommend the early introduction of nucleoside/nucleotide analogues (NAs) for all HBsAg-positive patients requiring immunosuppressive therapy. HBV prophylaxis must be introduced at least 7 d before therapy and it should be maintained for 6 mo to 1 year after completion of chemotherapy, as HBV reactivation may occur after chemotherapy is discontinued<sup>[3,4]</sup>. The European Crohn's and Colitis Organisation<sup>[57]</sup> also recommend an early introduction of NAs in HBsAg-positive IBD patients requiring immunosuppression, regardless of the number and type of immunosuppressants. However, it must be initiated between one and 3 wk prior to the introduction of immunosuppressive therapy and continued for 6 mo after its cessation<sup>[11,57]</sup>.

Lamivudine has been the most common drug used in this setting; however, resistance usually develops with prolonged use and has been detected in up to 30% of patients after 1 year and 70% after 5 years of treatment<sup>[66,67]</sup>. Resistance has also been described in patients on long-term anti-TNF therapy, which is associated with viral reactivation as reported by Esteve *et al.*<sup>[27]</sup> in a CD patient taking lamivudine for more than 5 years. Therefore, this agent may be appropriate for a short course of prophylaxis during chemotherapy but, as immunosuppressive medications for IBD may be required indefinitely, NAs with a lower propensity than lamivudine for generating drug-resistant mutations of HBV DNA must be chosen. Although alternative antiviral medications, such as tenofovir, adefovir, telbivudine and entecavir, have not been evaluated in prophylaxis for IBD patients, tenofovir and entecavir have the lowest rates of resistance with long-term use and should be preferred.

In cases in which lamivudine, adefovir or telbivudine are used, serum aminotransferase levels and HBV DNA levels must be closely followed for signs of drug resistance. Interferon- $\alpha$  must not be used for prophylaxis<sup>[57]</sup>.

In HBe-positive patients who are lacking HBsAg and have resolved hepatitis B, systematic use of antiviral prophylaxis in IBD patients is not recommended<sup>[1,21,49]</sup>. This approach differs from the recommendation for patients undergoing chemotherapy and particularly for rituximab, in which anti-viral prophylaxis is desirable<sup>[21-23,49,68]</sup>. Nevertheless, careful and constant monitoring of virological markers, including HBV DNA, is required in these patients during treatment for early recognition of viral reactivation and therapy with NAs at an early stage<sup>[69,70]</sup> (Figure 1).

In conclusion, new therapies in IBD patients are increasing the risk for HBV reactivation. All patients should be screened for HBV markers, preferably at diagnosis.

Current guidelines recommend screening with HBsAg and anti-HBs, but anti-HBc must also be considered so as to detect occult HBV. HBsAg positive patients requiring immunosuppressive therapy should receive antiviral treatment, regardless of HBV DNA level. Prophylaxis with nucleos(t)ide analogues must be introduced at least 3 wk before, but as immunosuppressive drugs may be required

indefinitely, NA with a low rate of resistance (tenofovir or entecavir) should be preferred. Patients with positive anti-HBc without HBsAg and undetectable viral DNA should be monitored closely for reactivation.

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