

## Hepatitis B and immunosuppressive therapies for chronic inflammatory diseases: When and how to apply prophylaxis, with a special focus on corticosteroid therapy

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are used in a more extensive and earlier way in patients with inflammatory bowel disease, rheumatic or dermatologic diseases. Although these drugs have shown a significant clinical benefit, the safety of these treatments is a challenge. Hepatitis B virus (HBV) reactivations have been reported widely, even including liver failure and death, and it represents a deep concern in these patients. Current guidelines recommend to preemptive therapy in patients with immunosuppressants in general, but preventive measures focused in patients with corticosteroids and inflammatory diseases are scarce. Screening for HBV infection should be done at diagnosis. The patients who test positive for hepatitis B surface antigen, but do not meet criteria for antiviral treatment must receive prophylaxis before undergoing immunosuppression, including corticosteroids at higher doses than prednisone 20 mg/d during more than two weeks. Tenofovir and entecavir are preferred than lamivudine because of their better resistance profile in long-term immunosuppressant treatments. There is not a strong evidence, to make a general recommendation on the necessity of prophylaxis therapy in patients with inflammatory diseases that are taking low doses of corticosteroids in short term basis or low systemic bioavailability corticosteroids such as budesonide or beclomethasone dipropionate. In these cases regularly HBV DNA monitoring is recommended, starting early antiviral therapy if DNA levels begin to rise. In patients with occult or resolved hepatitis the risk of reactivation is much lower, and excepting for Rituximab treatment, the prophylaxis is not necessary.

**Key words:** Hepatitis B virus; Inflammatory bowel disease; Rheumatic disease. Dermatologic diseases; Corticosteroids; Anti-tumor necrosis factor; Prophylaxis; Immunosuppressants

### Abstract

Currently immunosuppressive and biological agents

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**Core tip:** Few reviews have been published including data of the three more common inflammatory diseases that require immunosuppressive therapy: inflammatory bowel disease, rheumatic and dermatologic diseases. This paper is focused on the risk of reactivation of hepatitis B virus under immunosuppressants, and particularly corticosteroids. Although most of the guidelines do not specify the necessity of prophylaxis in case of monotherapy with corticosteroids, the specialists responsible of these patients are usually concerned about this issue. Moreover, the risk with low systemic bioavailability new corticosteroids has not been evaluated in previous reviews. This work summarizes the evidence of VHB reactivation in patients with inflammatory diseases: when and how to apply prophylaxis, with a special focus on "new" and "old" steroids.

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## INTRODUCTION

Hepatitis B virus (HBV) is a preventable viral infection, but it is estimated that 2 billion persons worldwide are infected, and a significant number of case reports and clinical studies have pointed the risk of reactivation of this infection in patients on immunosuppressive therapies<sup>[1,2]</sup> Immunosuppressive and biological treatments are used more and sooner, during long periods of time in patients with inflammatory diseases (ID), including inflammatory bowel disease (IBD), rheumatic or dermatologic diseases. Therefore, the safety of these treatments is a deep concern among gastroenterologist, rheumatologist, and dermatologist

## PREVALENCE OF HBV INFECTION IN PATIENTS WITH INFLAMMATORY DISEASES

The prevalence of the hepatitis B infection varies significantly worldwide, from 1%-2% in the Western countries, to more than 8% in Asia and Africa<sup>[3-5]</sup>.

Among patients with inflammatory diseases, those with IBD are assumed to have a higher risk of HBV infection because of the potential nosocomial transmission<sup>[6]</sup>. Biancone *et al*<sup>[7]</sup> found that IBD population had higher prevalence of hepatitis B surface antibody (HBsAb) than controls<sup>[7]</sup>, and studies conducted in endemic areas have reported a rate of present and past HBV infection of 40%<sup>[8]</sup>. Conversely, recent researches in Spain and France describe

exposure rates similar to the general population<sup>[9,10]</sup>, while Kim *et al*<sup>[11]</sup>, in South Korea, cannot find IBD as a risk factor for HBV, with a reported prevalence of hepatitis B surface antigen (HBsAg) of 3.7% in IBD vs 4.4% in the control group<sup>[11]</sup>.

In rheumatic diseases, the HBV status has also been evaluated. Irish investigators identified in a cohort of 200 rheumatoid arthritis (RA) patients only 4 cases with positive hepatitis B core antibody (HBcAb) and 11 with positive HBsAb, with no cases of positive HBsAg<sup>[12]</sup>. The prevalence of concurrent chronic hepatitis B infection in a cohort of RA patients in China was 11.2%, consistent with the prevalence in the general population<sup>[13]</sup>, although the reported rate of HBsAg in ankylosing spondylitis (AS) by Zheng *et al*<sup>[14]</sup> was 25.4%, higher than in the general population or patients with other spondyloarthropathies and RA. In Japan, where approximately 20% Japanese individuals are infected with HBV, HBsAg and HBcAb positive occurred in 0.7% and 25.6% of patients with RA<sup>[15]</sup>.

There are very few studies to determinate the prevalence of HBV infection in psoriasis and no significant differences between these patients and general population have been found<sup>[16]</sup>.

Therefore, we cannot say that ID patients are a great risk population for HBV infection, at least according to the more recent research. The Table 1 summarizes some of the more relevant studies that have evaluated the prevalence of HBV in patients with inflammatory diseases.

## DEFINITIONS OF HEPATITIS B INFECTION AND REACTIVATION

The exposure to HBV can be divided broadly by the viral load and the liver biopsy into three categories: (1) active chronic HBV, characterized by an elevated serum alanine transaminase (ALT) (usually more than twice the upper limit of normal) and DNA levels above 2000 IU/mL; (2) inactive hepatitis B carrier, defined by low HBV DNA levels, typically < 2000 IU/mL, and normal ALT. There is not a significant necroinflammatory activity on the liver biopsy; and (3) resolved HBV infection. These patients are characterized by negative HBsAg and positive HBsAb. Patients with occult HBV infection (OBI) test positive only for HBcAb<sup>[17]</sup>.

HBV reactivation is the reappearance of active necroinflammatory disease, marked by a 1.5-2-fold increase in ALT levels and DNA viral load > 2000 IU/mL in an inactive hepatitis B carrier, or a positivation from a previously undetectable DNA in an individual with a resolved hepatitis B<sup>[18,19]</sup>.

## EFFECT OF IMMUNOSUPPRESSIVE THERAPY ON HBV INFECTION

The HBV-induced liver inflammation is predominantly immune mediated: the host immune response

**Table 1** Studies evaluating the prevalence of hepatitis B virus infection in patients with inflammatory diseases

Ref.	Disease	Country	Publication year	Number patients	HBcAb	HBsAg
Biancone <i>et al</i> <sup>[7]</sup>	IBD	Italy	2001	494	UC 11.5% CD 11%	UC 0.64% CD 2.1%
Loras <i>et al</i> <sup>[9]</sup>	IBD	Spain	2009	2056	UC 8% CD 7.1%	UC 0.8% CD 0.6%
Chevaux <i>et al</i> <sup>[10]</sup>	IBD	France	2010	315	UC 1.6% CD 2.8%	UC 1.59% CD 0.79%
Huang <i>et al</i> <sup>[3]</sup>	IBD	China	2014	714	UC 41.6% CD 39.8%	UC 5.7% CD 5.3%
Kim <i>et al</i> <sup>[11]</sup>	IBD	South Korea	2014	513		UC 4.1% CD 3.3%
Zou <i>et al</i> <sup>[13]</sup>	RA	China	2013	223	11.2%	
Watanabe <i>et al</i> <sup>[15]</sup>	RA	Japan	2014	7650	25.6%	0.7%
Conway <i>et al</i> <sup>[12]</sup>	RA	Ireland	2014	200	2%	0%
Zheng <i>et al</i> <sup>[14]</sup>	AS	China	2011	439		25.4%
Cohen <i>et al</i> <sup>[16]</sup>	Psoriasis	Israel	2010	12502		0.74%

IBD: Inflammatory bowel disease; HBcAb: Hepatitis B core antibody; HBsAg: Hepatitis B surface antigen; RA: Rheumatoid arthritis; AS: Ankylosing spondylitis.

causes a hepatocellular damage following the HBV replication, which can result in an acute or chronic liver necroinflammation.

Immunosuppressants lead to an increase in DNA viral due to both a effect on the host immune response, as to a stimulatory effect of these drugs on hepatitis B virus<sup>[20]</sup>. The corticosteroids may increase the expression of HBV through a glucocorticoid-responsive element, which has been detected in viral genome, and stimulates viral replication in patients under these treatments<sup>[21]</sup>.

On the other hand, tumoral necrosis factor (TNF)  $\alpha$  and interferon gamma (IFN $\gamma$ ) are important in the clearance of HBV from infected hepatocytes, so the use of anti-TNF drugs in patients with chronic HBV infections may result in an increase in viral replication<sup>[22,23]</sup>.

Despite the increase in viral replication, the major damage hardly ever appears at the time of maximal immunosuppression and usually occurs once the immunosuppressive therapy is withdrawn, during the phase of immune reconstitution, when the immune system is able to destroy the hepatitis B-infected hepatocytes, producing the liver disease<sup>[5,24]</sup>. Clinically these exacerbations can vary, ranging from a subclinical or asymptomatic course to a severe acute hepatitis and even death<sup>[25]</sup>.

## HBV REACTIVATIONS IN PATIENTS WITH INFLAMMATORY DISEASES

In ID patients the risk of hepatitis B reactivation is highest with the use of monoclonal antibodies anti-CD20 (rituximab)<sup>[26]</sup>, but it may also be fatal in inactive hepatitis B carriers patients undergoing other

immunosuppressant treatments<sup>[27]</sup>. Cases of HBV reactivation have been reported in RA patients treated with methotrexate (MTX) generally at doses lower than 10 mg/wk<sup>[28]</sup>, and anti-TNF agents, specially with IFX, but also with adalimumab and etanercept<sup>[29-31]</sup>.

Oshima *et al*<sup>[32]</sup> measured the risk of hepatitis B with anti rheumatic drugs and found a significant association between them and the occurrence of hepatitis exacerbation {corticosteroids [OR = 2.3 (1.3-4)], MTX: [4.9 (3.9-6.0)] and rituximab: [7.2 (5.3-9.9)]}<sup>[32]</sup>. Lee *et al*<sup>[33]</sup> and Nakamura *et al*<sup>[34]</sup> reported an incidence of viral reactivations of 5.3% and 12% in the patients under immunosuppressive treatment and inactive viral infection<sup>[33,34]</sup>.

Regarding IBD, reported cases of reactivation of HBV with IFX have been extensively reviewed elsewhere<sup>[35-38]</sup>. Most of them have occurred in patients with co-treatment with immunomodulators such as azathioprine or MTX. The Spanish REPENTINA study showed that no single drug was specifically involved, and the risk seems to be associated with the intensity of immunosuppression<sup>[39,40]</sup>.

Case reports of HBV exacerbation in severe psoriasis patients have also been published<sup>[41]</sup>. In a recent review in patients with rheumatic, digestive, and dermatologic autoimmune diseases, treated with any of the anti-TNF inhibitors, by Pérez-Alvarez *et al*<sup>[42]</sup> HBV reactivation was observed in 39% of hepatitis B carriers in hepatitis B carriers. Reactivations were more frequent in patients previously treated with other immunosuppressive agents (96% vs 70%,  $P = 0.033$ ) and less in those who received antiviral prophylaxis (23% vs 62%,  $P = 0.003$ ).

Although anti-TNFs are the most common biological therapy in patients with ID, human IgG1k monoclonal antibody of interleukin-12/23 (ustekinumab) has become an emerging therapy, especially in chronic psoriasis, but also in IBD. There are scarce data about the safety of ustekinumab and the relationship between IL-12 or IL-23 and HBV, but some cases of reactivations have been described<sup>[2,43,44]</sup>.

Regarding patients with resolved HBV or OBI, the risk is much lower. Reactivations following chemotherapy or potent immunosuppressive drugs such as Rituximab have been reported specially on the onco-haematological field<sup>[13,45]</sup>, and although some cases have also been published with anti-TNF therapy, the rate is not relevant<sup>[46]</sup>. Tamori *et al*<sup>[47]</sup> described the reactivation risk in 50 patients, with positive results for hepatitis B core antibody, treated with immunosuppressants for rheumatic diseases: the reactivation was 10 times more likely in those with HBsAg positive than in the HBsAg negative grupo (20% vs 2%)<sup>[47]</sup>.

Finally, Cassano *et al*<sup>[48]</sup> analyzed 62 psoriatic patients with occult viral infection, treated with anti-TNFs agents. There were no signs of HBV activation after a period of 4 years, which supports the safety of the use of immunosuppressant drugs (others than

**Table 2** Hepatitis B virus reactivations in patients treated with steroids

Ref.	Disease	Study	Patients (n)	HBV status (n)	Pre-emptive therapy	HBV reactivations (n)
Cheng <i>et al</i> <sup>[58]</sup>	Autoimmune diseases	Case report	2	CHB (1) RS (1)	No	2
Nakanishi <i>et al</i> <sup>[57]</sup>	Polymyositis	Case report	1	CHB	No	1
Zanati <i>et al</i> <sup>[59]</sup>	Mixed connective tissue disease	Case report	1	CHB	No	1
Bae <i>et al</i> <sup>[60]</sup>	Rheumatoid arthritis	Case report	1	CHB	No	1
Li <i>et al</i> <sup>[61]</sup>	Idiopathic nephrotic syndrome	Prospective	41	CHB (41)	No	21
Yang <i>et al</i> <sup>[62]</sup>	Connective tissue disease	Retrospective	98	CHB (21) Not applied (77)	No	4
Loras <i>et al</i> <sup>[39]</sup>	IBD	Retrospective	25	CHB	No	6

Adapted from Xuan *et al*<sup>[63]</sup>. CHB: Chronic hepatitis B, inactive carriers included; RS: Resolved infection; HBV: Hepatitis B virus.

rituximab) in this scenario<sup>[48]</sup>.

## CORTICOSTEROIDS AND IMMUNOSUPPRESSION

The risk of infections with corticosteroids are proved to be increased with the dose<sup>[49]</sup>. Although it is not clearly defined, a dose equivalent to either 2 mg/kg of body weight or a total of 20 mg/d of prednisone are accepted to suppress significantly the immune system in treatments longer than two weeks<sup>[50-52]</sup>.

The Consortium of Rheumatology Researchers of North America evaluated the risk for all infectious events, which were increased with prednisone 10 mg/d (incidence rate ratio relative:1.30; 95%CI: 1.11-1.53) whilst any dose increased the risk of opportunistic infections<sup>[53]</sup>.

Concerning IBD population, there are no precise data on the dose of corticosteroids associated with the increased risk, but Rahier *et al*<sup>[25]</sup> in the *Second* European evidence-based Consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease, indicate that doses greater than 20 mg/d of prednisolone in adults are immunosuppressive and increase the percentage of events<sup>[25]</sup>.

Beyond that, the combination of two or three of immunosuppressant drugs enhances the probability of infections<sup>[54,55]</sup>.

### Corticosteroids and HBV reactivation

First reactivation was described by Wands *et al*<sup>[56]</sup> in 1975, in 20 patients with lymphoproliferative and myeloproliferative disorders receiving chemotherapy.

Subsequently, other cases were communicated in rheumatic and autoimmune diseases: Nakanishi *et al*<sup>[57]</sup> and Cheng *et al*<sup>[58]</sup> reported HBV reactivations after high dose of steroids in monotherapy. None of the cases had received prophylaxis for HBV, and developed clinical disease in 4, 5 and 9 mo after the beginning of the treatment. Zanati *et al*<sup>[59]</sup> and Bae *et al*<sup>[60]</sup> have also described two fatal cases of HBV reactivations in patients with connective tissue diseases treated with steroids and chloroquine.

Another prospective study, carried in 41 Chinese adults with idiopathic nephrotic syndrome and inactive hepatitis B, compared standard doses of prednisone vs lower doses of prednisone plus mycophenolate mofetil (MMF)<sup>[61]</sup>. Without pre-emptive therapy, the risk of exacerbation was lower in MMF-prednisone regimen than the group with prednisone in monotherapy, reflecting the major effect of higher doses on the viral reactivation.

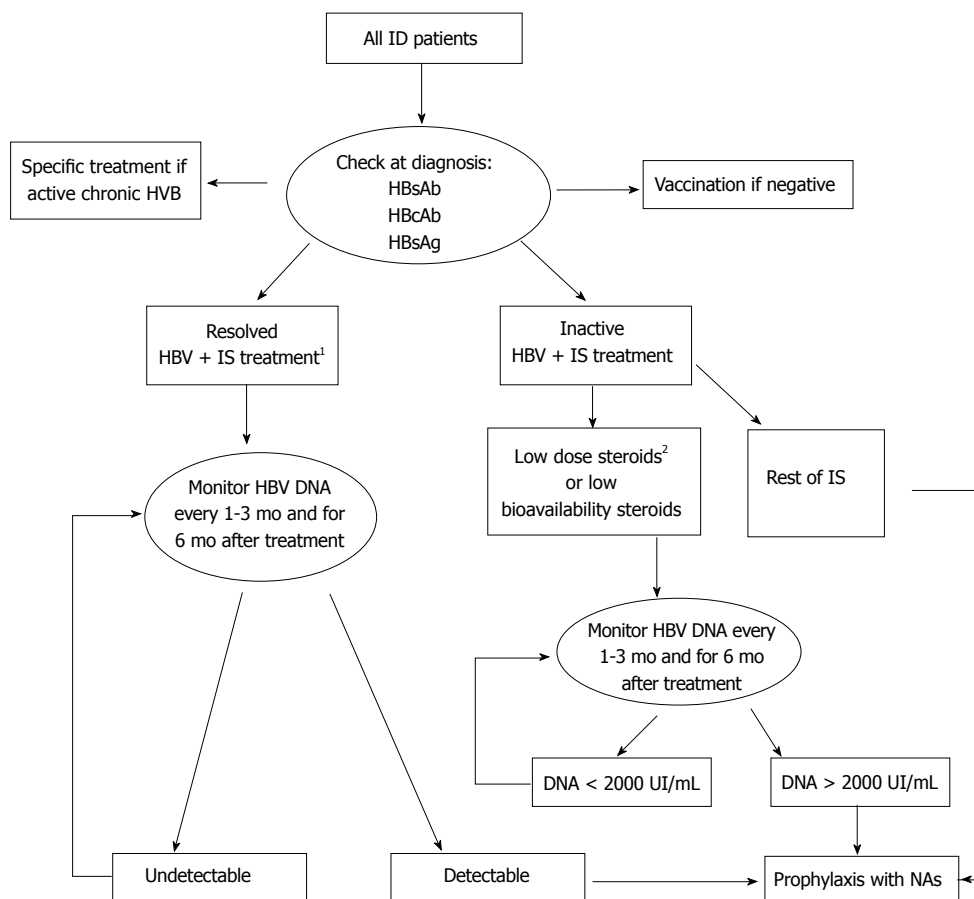
Yang *et al*<sup>[62]</sup> identified in a retrospective study, four cases of viral hepatitis flares in HBV carriers, who received at least 6 mo of high doses of systemic corticosteroid for connective tissue diseases<sup>[62]</sup>, and resulted in a mortality of fifty percent.

Finally, Xuan *et al*<sup>[63]</sup> have reviewed 30 cases of reactivation after steroids, in monotherapy or combined with other therapies, in 144 patients with rheumatic diseases. The mean time to reactivations was 9.8 mo. Although the findings indicate that the risk of hepatitis reactivation mostly relies on the prednisone doses, as some cases of HBV reactivation have occurred with low-dose-prednisone therapies, caution is advisable<sup>[60]</sup>.

In IBD there have also been reports of reactivation in patients under corticosteroids, with or without azathioprine or anti-TNF therapy, even resulting in severe acute hepatitis<sup>[6,64,65]</sup>. The Spanish REPENTINA study describes 6 cases of HBV reactivation in IBD patients during conventional immunosuppressive therapy, two of them with prednisone in monotherapy. Fifty percent of the cases resulted in liver failure and one of them required a liver transplantation<sup>[39]</sup>. The Table 2 reflects the cases of HBV reactivation with steroid therapy.

### Reactivation of HBV and "new" corticosteroids

The typically acting oral steroids are agents characterized by a low systemic bioavailability due to an important first-pass liver metabolism. So, the typical adverse effects of steroids are partially avoided because of a lower concentration of the drug in plasma<sup>[66]</sup>. The most representative are beclometasone dipropionate (BDP) and budesonide. Many studies have reported their efficacy compared to placebo,



**Figure 1** Algorithm suggested for the management of patients with inflammatory diseases and hepatitis B virus infection. <sup>1</sup>Except Rituximab, in which antiviral prophylaxis is desirable; <sup>2</sup>Low dose steroids  $\leq$  20 mg/d prednisone. Adapted from Lopez-Serrano *et al.*<sup>[77]</sup>. ID: Inflammatory diseases; IS: Immunosuppressants (steroids, thiopurines, methotrexate and biologics); NAs: Nucleoside/nucleotide analogues; HBcAb: Hepatitis B core antibody; HBsAg: Hepatitis B surface antigen; Low bioavailability steroids: Budesonide or beclometasone dipropionate; HBV: Hepatitis B virus.

conventional steroids and 5-ASA<sup>[67-70]</sup>. Nunes *et al.*<sup>[71]</sup> reported the Spanish experience of oral BDP in a retrospective and multicenter study that included more than four hundred patients with active UC. Mild secondary effects were described in 7.6% of the cases, but no serious events either cases of HBV reactivations were identified.

Lichtenstein *et al.*<sup>[72]</sup> reviewed five trials evaluating budesonide for up to 1 year for mild-to-moderate CD compared to placebo. Budesonide 6 mg/d was found to be significantly associated with mild infections ( $P = 0.023$ ), but clinically important events were rare, and no HBV reactivations were observed.

## PROPHYLAXIS AGAINST HEPATITIS B REACTIVATION

The aim of the diverse guidelines is to provide clear recommendations for clinical practice. Before 2005 there were no recommendations for HBV and HCV screening in IBD or rheumatic patients requiring immunosuppression<sup>[73]</sup>. The appropriate time to do hepatitis B serologic tests is at diagnosis, better than the moment of considering immunosuppression<sup>[74-77]</sup>.

The tests must include HBsAb, HBsAg, and HBcAb, in order to detect also OBI, and HBV vaccination or HBV-DNA quantification must be done depending on the results<sup>[25]</sup>.

Patients with active chronic HBV should receive the antiviral treatment applicable to immunocompetent patients, but this is not the goal of this review.

### Prophylaxis in hepatitis B resolved infection

Excepting rituximab, there is no evidence for systematic anti-viral prophylaxis in resolved or OBI in patients on immunosuppressants, taking into account that the HBV reactivation occurs rarely<sup>[78]</sup>. These patients must be followed closely during therapy (every 1-3 mo, and for 6 mo after stopping treatment), and considered for prophylactic therapy according to DNA levels<sup>[5]</sup> (Figure 1).

### Prophylaxis in inactive hepatitis B carriers

The American Association for the Study of Liver Diseases and the European Association for the Study of the Liver recommend the early introduction of pre-emptive therapy in those HBsAg carriers which are going to start immunosuppressive therapy,

including immunomodulators, biologic therapy and corticosteroids<sup>[74,75]</sup>. As we have commented previously, a dose of prednisone higher than 20 mg/d appears to be sufficiently immunosuppressive, in treatments longer than two weeks, so that prophylaxis must be considered. It must be introduced 1-3 wk before therapy and continue for 6 mo to 1 year after withdrawal<sup>[77,79,80]</sup>.

Apart from cases reviews, there is no strong evidence to make this recommendation in patients with ID and low doses of corticosteroids in short term basis. More conservative management advises to monitor regularly HBV DNA and to start early antiviral therapy if DNA level arises<sup>[6,81,82]</sup>. The same recommendations can be made in the case of the low systemic bioavailability steroids (budesonide and BPD).

### Which antiviral drug must we choose?

Lamivudine has been the most frequent agent used agent in this scenario, having proved to reduce the reactivation risk and the associated mortality and morbidity. However, Lamivudine resistance develops in 53%-76% of patients after 3 years of treatment, therefore, this agent is only appropriate when a short course of therapy is needed. As immunosuppressants for ID usually are used for long term, nucleoside/nucleotide analogues (NAs) with a lower rate of resistance must be considered. Tenofovir and entecavir have a higher barrier to resistance, and should be used if treatments longer than 12 mo are planned<sup>[6,76,77,82,83]</sup>.

In those patients with OBI with a high risk of reactivation, lamivudine may still have a role, because of its low cost, and the low or absent HBV viremia in these cases<sup>[76,78]</sup>. Alternative antiviral medications for lamivudine would be adefovir and telbivudine<sup>[20]</sup>. In all cases, but more closely if lamivudine, adefovir or telbivudine are used, serum AST/ALT levels and hepatitis B viral load must be monitored every 3 or 6 mo.

In conclusion, HBV reactivations are not uncommon in inactive HBV patients treated with immunosuppressive therapy for inflammatory diseases. Current guidelines highly recommend prophylaxis in case of immunosuppressive therapy, including patients receiving steroids in monotherapy. However, steroids at low doses, treatments shorter than two weeks and low bioavailability steroids are unlikely to need prophylaxis, although studies are lacking in this setting. These patients and those with occult or resolved HBV precise regularly HBV DNA monitoring during immunosuppressant therapy in order to detect reactivations. Entecavir or tenofovir are recommended as the optimal agents against HBV reactivation.

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