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Hepatitis B and C virus reactivation in immunosuppressed patients with inflammatory bowel disease

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Abstract

In recent years, a number of case reports and clinical studies have highlighted the risk of hepatitis B and C virus reactivation in patients with inflammatory bowel disease who are treated with immunosuppressive drugs. The cases of viral hepatitis reactivation that have been reported are characterized by a wide range of clinical manifestations, from viremia without clinically relevant manifestations to fulminant life-threatening hepatitis. The development and dissemination of biological immunosuppressive drugs have led to a significant increase in the number of reports of interest to physicians in a variety of clinical settings. On this topic, there have been a number of published guidelines and reviews that have collected the available evidence, providing recommendations on prophylactic and therapeutic strategies and methods for monitoring patients at risk. However, it should be noted that, to date, very few clinical studies have been published, and most of the recommendations have been borrowed from other

clinical settings. The published studies are mostly retrospective and are based on very heterogeneous populations, using different therapeutic and prophylactic regimens and obtaining conflicting results. Thus, it seems clear that it is desirable to concentrate our efforts on prospective studies, not conducting further reviews of the literature in the continued absence of new evidence.

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Key words: Inflammatory bowel disease; Biological agents; Hepatitis B virus reactivation; Hepatitis C virus reactivation; Prophylaxis

Core tip: Our review focused on the redundancy of papers on hepatitis B virus and hepatitis C virus reactivation in patients undergoing immunosuppressive therapy. However, we emphasize that, to date, very few clinical studies have been published, and most of them were retrospective with conflicting results. Thus, it is essential to conduct prospective studies before performing additional reviews of the literature.

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INTRODUCTION

In recent years, a significant number of warnings have been given about the risk of hepatitis B and C reactivation.

tion in patients receiving immunosuppressive therapy in different clinical settings (oncology, hematology, solid organ transplant, rheumatology, gastroenterology, and dermatology).

In particular, a number of case reports and clinical studies have highlighted the risk of hepatitis virus B and C reactivation in patients with inflammatory bowel disease (IBD) treated with immunosuppressive drugs^[1-7].

The cases of viral hepatitis reactivation that have been reported are characterized by a wide range of clinical manifestations, from viremia without clinical relevant manifestations to fulminant life threatening hepatitis.

The risk and severity of clinical reactivation seems to be related to the type of immunosuppressive drug administered (steroids, traditional immunosuppressants, or biologics). The various reports and clinical studies on this topic describe and analyze patient populations subjected to different treatment regimens that are not comparable. Moreover, these studies have heterogeneous results and conclusions^[8-13].

The magnitude of the “reactivation “ problem seems much more relevant to the hepatitis B virus (HBV) than to the hepatitis C virus (HCV). To date, many reviews comparing few clinical trials have been published on this issue. Among the clinical trials, there was only one prospective study. All of the studies were conducted in different populations with different methods and drawing varying conclusions. Furthermore, the definitions of HBV and HCV reactivations used vary significantly among these studies. Some studies have considered only the increase of viral load, while others have considered the increased viral load in association with elevated levels of aminotransferases.

While some recommendations may appear “evidence-based”, such as prophylaxis for hepatitis B surface antigen positive (HBsAg+) patients receiving immunosuppressive therapy, there are large gray areas, indicating the risk of reactivation in patients with hepatitis B core antibody (HBcAb) isolated or and HCV positivity.

As mentioned above, there is currently not enough strong evidence regarding the prevalence and clinical impact of hepatitis B and C virus reactivation in patients with IBD who are receiving immunosuppressive therapy. This finding calls for the development of prospective clinical trials that can respond to the growing demand of evidence on this issue^[14,15].

IMMUNOSUPPRESSIVE THERAPY IN IBD

The ideal therapeutic approach to IBD should be aimed at inducing and maintaining long-term clinical remission with the minimal use of steroids and surgical interventions; this end-point is particularly important for patients affected by Crohn's disease (CD).

However, about half of IBD cases show a steroid-dependent or steroid-refractory clinical course^[16,17]. Currently, a traditional immunosuppressive therapeutic regimen is indicated for these patients and is mainly represented

by the use of azathioprine and 6-mercaptopurine, even if this regimen produces a low percentage of clinical remission (50%) in the treated population^[18,19]. Other potentially effective immune-suppressors are methotrexate, cyclosporine and tacrolimus. These drugs are rarely used in this setting due to the lack of significant evidence on their efficacy and are used in clinical practice for steroid-refractory ulcerative colitis (UC), as well as anti-tumor necrosis factor alpha (anti-TNF α) agents^[20-30].

IBD patients who are refractory or intolerant to azathioprine are the main candidates for biological anti-TNF α drugs (*i.e.*, adalimumab and infliximab).

Infliximab has proven to be an effective drug in inducing and maintaining clinical remission in refractory luminal and fistulizing CD, with a remission rate of approximately 50%^[29,31-36]. The efficacy of infliximab in treating UC is less impressive than in CD. However, the ACT-1 study^[37] reported an efficacy of 39% and 20% for infliximab in inducing the remission of steroid-dependent UC at weeks 8 and 54, respectively. Furthermore, this drug can avoid the 3-mo need for colectomy in approximately 65% of patients who experience a severe attack of UC^[38,39].

At present, adalimumab, a fully human recombinant anti-TNF α antibody, is approved for the treatment of CD and UC. This drug, administered by subcutaneous injection, has been efficient in inducing and maintaining remission in CD, with a 40% remission rate at week 56^[40,41]. Therefore, similar to infliximab, adalimumab has proven to be valuable in reducing the need for steroids and surgery^[42].

In view of their high efficacy, it has also been suggested that biologics could be used in the early phases of IBD in accordance with a top-down therapeutic strategy^[43], particularly for patients with a poor prognosis and factors implicating a potentially aggressive disease (*i.e.*, young age, smoking, perianal/rectal disease in CD, extensive small bowel involvement, extra-intestinal manifestations, and steroid use at diagnosis)^[42,44-47].

PREVALENCE OF HBV AND HCV INFECTION IN PATIENTS WITH IBD

The prevalence of HBV infection varies greatly throughout the world, from the low rate of < 1% to the moderate rate of 1%-2% in Western countries, towards a much higher rate of > 8% in Asia and in most parts of Africa. The dramatic progress in controlling the spread of HBV in Western countries is prevalently due to the implementation of the vaccination and the adoption of satisfactory measures in preventing HBV transmission^[48-53].

Patients with IBD are considered at risk of HBV and HCV infection because of the frequent need for surgical, endoscopic and transfusion procedures, suggesting the existence of nosocomial transmission. On the other hand, the magnitude of this risk is unknown because there are conflicting reviews and little information on this topic.

Five studies from Italy^[8,54], France^[49], Spain^[55] and China^[51] have evaluated the prevalence of HBV and HCV infections in consecutive series of patients with IBD. Between 1997 and 1999, 332 patients affected by CD were enrolled in an Italian case-control study published in early 2000. The prevalence of HBsAg, HBcAb and HCV in this cohort was 2.1%, 10.9% and 7.4%, respectively. Ten years later, the prevalence of HBsAg and HCV was approximately 1% (Table 1) in 315, 2076 and 301 consecutive subjects in three series of French, Spanish and Italian IBD patients. HBcAb positivity was present in 8/315 (2.54%) of patients in the French study (3 HBsAg+ and HBcAb+; 2 isolated HBcAb+; and 3 HBcAb+ and anti-HBs+); in 154/2056 (7.49%) of patients in the Spanish study; and in 22/301 (7.31%) of patients in the Italian study.

Therefore, the prevalence of HBV and HCV infection in IBD patients seems to be lower than expected, similar to the general population. These results indicate that IBD patients in Western European countries should no longer be considered as a risk group for HBV or HCV infection.

However, a recent study conducted in China on 714 IBD patients showed that the prevalence of HBV infection in IBD patients was higher than reported in the control group. Indeed, the cumulative prevalence of HBsAg and HBcAb was 40.62% *vs* 27.58% in non-IBD patients. The prevalence of HCV infection was similar to that found in non-IBD patients (0.42% *vs* 0.36%).

HBV INFECTION

Mechanism of reactivation

From an immunological point of view, a hepatitis flare rarely starts during the phase of maximal immunosuppression. The majority of reported HBV reactivations matured at the time of the withdrawing or tapering of immunosuppressive therapy, when the immune system has been able to react to the viral replication and to destroy infected hepatocytes^[56].

In this perspective, any deficiency of the immune response to infections caused by immunosuppressive/chemotherapeutic drugs would play a crucial role in disease progression.

In addition, several *in vitro* and *in vivo* animal studies have demonstrated that TNF- α plays a key role in clearing HBV from infected hepatocytes. Hepatitis B viral HBx proteins sensitize the cells to apoptotic killing by TNF, which is secreted by cytotoxic T lymphocytes, together with Interferon- γ (IFN- γ). Both TNF and IFN- γ clear HBV replicative intermediates from the cytoplasm and covalently close circular DNA from the nuclei of infected hepatocytes^[57,58].

Based on these results, it is possible that the use of anti-TNF α drugs in patients with chronic HBV infections could cause an increase in viral replication, leading to liver immune-mediated damage when the inhibitory effect of therapy disappears^[59].

According to this pathogenic model, the risk of HBV reactivation is closely related to the level of immunosuppression achieved, which changes significantly based on the immunomodulatory agents used during the therapy. Stronger immunosuppression may lead to increased viral replication; consequently, a more severe clinical reactivation may occur when immunosuppressive therapy is discontinued^[56].

Immunosuppressive therapy and risk of reactivation in HBsAg positive patients

The reactivation of HBV is an important concern for patients taking immunosuppressants because of the many ways it can affect the body, from a subtle shift in serum aminotransferase levels to fulminant hepatic failure and/or death.

The reactivation of HBV infection (with liver dysfunction, including fulminant hepatitis) is a well-described complication of immunosuppression in the setting of organ transplantation or cancer chemotherapy, occurring in approximately 50% of patients for whom concomitant anti-viral therapy is not used. Mortality from fulminant liver failure after the reactivation of HBV in patients receiving chemotherapy is reported in 4%-60% of cases. The traditional immunosuppressive drugs used in the management of IBD patients include the following: corticosteroids; thiopurines: azathioprine and 6-mercaptopurine; calcineurin inhibitors; cyclosporin and tacrolimus; and methotrexate. Moreover, in the past decade, these biological agents, especially TNF α inhibitors, have been used worldwide and are particularly beneficial in the management of complex and fistulizing diseases^[19-23,31-36].

From a pathogenic perspective, the risk of HBV reactivation is closely related to the levels of immunosuppression. The use of conventional immunosuppressive drugs determines low levels of immunosuppression and does not seem to be associated with the risk of HBV reactivation; this claim is supported by the results of only one study^[9]. In a series of 332 CD patients, only 4 HBsAg positive patients were treated with conventional immunosuppressive drugs (2 with azathioprine and 2 with corticosteroids) and followed-up for at least 1 year. No influence on the clinical course of HBV infection and no episodes of viral or biochemical reactivation were observed in this series of patients over the follow-up of 12 mo.

Notably, only a few cases (4 cases) of HBV reactivation during conventional immunosuppressive therapy (prednisone and azathioprine) resulting in fulminant hepatic failure has been reported in the literature^[11,60].

In recent years, a growing number of cases of HBV reactivation among patients with IBD treated with TNF- α -inhibitors have been described. The available data are limited to a small number of single case reports and a very small series of consecutive patients^[10,12-13,60-65].

Eight case reports describe the use of anti-TNF α drugs in patients with IBD infected with HBV (HBsAg+

Table 1 Virologic and clinical outcomes of hepatitis B virus infection in patients with inflammatory bowel disease undergoing immunosuppressive therapy

Ref.	Disease	Age/ sex	HBsAg status	HBV-DNA before therapy	Anti- TNF α	Contemporary drugs	LAM prophylaxis	HBV-DNA reactivation	Biochemical reactivation
Esteve <i>et al</i> ^[66]	CD	34 M	+ IC	NA	IFX	AZT	No	Yes	ALT 2089
	CD	38 M	+ IC	NA	IFX	AZT	No	10.400 pg/mL Yes	AST 1561 ALT 2225
del Valle <i>et al</i> ^[61]	CD	26 M	+ CH	Positive	IFX	AZT	Yes	9000 pg/mL	AST 2146
	CD	40 M	+ CH	Positive	IFX	AZT	No	No worsening	No
Ueno <i>et al</i> ^[64]	CD	28 F	+ IC	NA	IFX	AZT	No	Yes	ALT 43
Millonig <i>et al</i> ^[12]	CD	50 M	+ IC	Positive	IFX	AZT	No	4.5 LEG/mL Yes	AST 64 ALT 983/50
Colbert <i>et al</i> ^[10]	CD	54 M	+ IC	20 IU/mL NA	IFX	AZT	No	38000000 UI/mL Yes	AST 413/50 ALT 124
Madonia <i>et al</i> ^[13]	CD	41 F	- OC	NA	IFX	Steroids	No	1.604 pg/mL Yes	AST 143 ALT \times 10 UNL
Ojira <i>et al</i> ^[63]	CD	43 F	+ IC	NA	IFX	AZT	No	Yes	ALT 239
Zeitz <i>et al</i> ^[11]	UC	43 M	NA	NA		Steroids + AZT	No	5.4 LGE/mL Yes	AST 145 ALT 3396
								110000000 UI/mL	AST 2193

CD: Crohn's disease; UC: Ulcerative Colitis; IC: Inactive carrier; OC: Occult carrier; NA: Not available; CH: Chronic hepatitis; IFX: Infliximab; AZT: Azathioprine; LGE: Logarithm genome equivalent; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus; TNF α : Tumor necrosis factor alpha; LAM: Lipoarabinomannan.

inactive carriers). All were affected by CD, and 7 out of 8 did not receive immunoprophylaxis. Only one patient received lamivudine as a prophylactic treatment. Six out of 7 showed HBV reactivation with a wide range of outcomes, ranging from a modest increase in the viral load and ALT levels to fatal hepatitis. Interestingly, the only patient who received prophylactic treatment did not experience viral, biochemical or clinical reactivation during the 6 mo follow-up^[66]. The duration of anti-TNF α therapy before HBV relapse varied from a single infusion to many months of treatment, and all of the episodes of reactivation were observed in patients receiving infliximab and other immunosuppressive drugs at the same time (Table 1). No reports are available in patients using adalimumab.

Recently, Loras *et al*^[55] recorded all clinical information from IBD patients with HBV and HCV infections in 19 Spanish hospitals. HBV reactivation was observed in 9 out of 25 (36%) HBsAg+ patients. All but two cases were treated with simultaneous immunosuppressors [steroid + azathioprine (4 cases) and infliximab + azathioprine (3 cases)]. In contrast, the patients without reactivation were only treated with one immunosuppressant and/or received prophylactic antiviral treatment. In 6 out of the 9 cases (66%), HBV reactivation caused severe hepatic failure.

On the contrary, Morisco *et al*^[55] conducted a retrospective multicenter study, including 5096 patients with IBD. HBV reactivation was observed in only 1 out of 6 (16%) HBsAg+ patients undergoing immunosuppressive therapy. A combined immunosuppressive therapy had been administered in all cases of HBV reactivation (Table 2).

Immunosuppressive therapy and risk of reactivation in HBsAg negative/HBcAb positive carriers

HBsAg negative and HBcAb positive IBD patients seem to have a low risk of HBsAg seroreversion and hepatitis flares. Indeed, in opposition to the results found in other clinical settings, only one case of HBV reactivation has been described in an IBD patient^[13]. A female CD patient was treated with 25 mg/d of prednisone and infliximab for the relapse of disease after an unsatisfactory remission with conventional therapy (steroids, ciprofloxacin, metronidazole, and methotrexate). After a month of treatment with infliximab and steroids, the patient's aminotransferases increased (10 times over the upper normal limit), together with the emergence of HBsAg, hepatitis Be antibody, HBcAb, IgM HBcAb, and HBV-DNA positivity in the serum.

HCV

Immunosuppressive therapy and risk of reactivation

To date, there is no conclusive information on the safety of immunosuppressive or immunomodulator drugs in HCV among IBD patients. These patients appear to be at low risk, although long-term safety studies are needed.

There are several interesting concerns regarding immunosuppressive treatment for IBD in patients with HCV infection. For example, prednisone, which is frequently used to treat acute exacerbations of intestinal diseases, may negatively affect HCV infection by increasing the viral load^[67-69].

On the other hand, anti-TNF α drugs seem to reduce inflammation through TNF α inhibition, playing a role in the pathogenesis of HCV^[70].

Table 2 Reactivation in patients with inflammatory bowel disease undergoing immunosuppressive therapy

Ref.	HBsAg+	HBcAb+	HCV+
Loras <i>et al</i> ^[60]	9/25	0/65	8/51
Morisco <i>et al</i> ^[65]	1/6	1/4	1/10
Papa <i>et al</i> ^[54]	0/1	0/22	0/4

HBsAg: Hepatitis B surface antigen; HBcAb: Hepatitis B core antibody; HCV: Hepatitis C virus.

Few studies have been performed to evaluate the safety of TNF α antagonist medications in IBD patients with HCV, and most of these are case reports or small case series^[54,55,65].

The larger series available on this topic show a low risk of hepatitis flares in these patients with a mild-moderate clinical course^[54,60,65]. Indeed, HCV reactivation was observed in 8/51 (15.7%) and in 1/10 (10%) HCV-RNA positive patients, respectively, by Loras *et al*^[60] and Morisco *et al*^[65]. All cases of reactivation had a very mild course, except for one patient, who died.

The deceased patient described by Loras *et al*^[60] and experienced severe liver failure. He died while receiving steroids. Importantly, he also had an occult HBV infection and was human immunodeficiency virus-positive.

SCREENING AND VACCINATION

Screening measures must be instituted in IBD patients. Recommendations are based on the potentially fatal consequences of HBV and HCV reactivation and the availability of safe and effective drugs to prevent these situations^[11].

HBV

The most recent guidelines of the European Crohn's and Colitis Organization (ECCO) on the management of opportunistic infections in IBD^[17] recommend that all IBD patients be tested for HBsAg, HBcAb and HBsAb to assess their infection or vaccination status; vaccination is recommended in all seronegative patients.

At present, only four studies have evaluated the HBV vaccination status of patients with IBD. Evidence of effective vaccination (positive anti-HBs and negative HBcAb) was only detected in 12%, 48.9%, 24% and 21.7% of the four cohorts of patients enrolled in Spain, France, Italy and China, respectively^[49,51,54,55]. No information about the adherence to HBV vaccination is available in the literature for other series of European patients with IBD.

HBV vaccination coverage significantly differs among European countries because the vaccination programs were started in different years and have been proposed for different target populations (newborns, adolescent and pre-adolescent subjects, only for high-risk groups, *etc.*)^[71].

As consequence, the determination of the infectious or vaccination status at the time of a diagnosis of IBD

seems to be appropriate. An administration of the vaccine in negative subjects (HBsAg, HBcAb and HBsAb negative) as soon as possible should progressively reduce the number of cases with problematic management. Improved adherence to the program of universal vaccination will reduce the need for screening in the future.

HCV

No recommendations have been proposed for HCV screening prior to starting immunomodulators by the ECCO guidelines^[72]. However, we do believe that HCV screening (including HCV antibodies and HCV-RNA if anti-HCV+) should be routinely performed upon the completion of liver function tests before starting immunosuppressive therapy. If positive, these tests should be performed again every 3 mo to carefully monitor the patient's status during immunosuppressive treatment.

With regard to the use of anti-TNF α agents, it is important to emphasize that their use should be evaluated on the basis of the clinical underlying condition of the patient. In particular, while the use of anti-TNF α in non-cirrhotic patients appears safe, it is contraindicated in patients with decompensated cirrhosis and should be used with caution in patients with compensated cirrhosis on a case-by-case basis, according to the benefit/risk ratio.

PROPHYLAXIS AND THERAPY

Several studies have reported a preventive effect of antiviral agents on hepatitis B reactivation during immunosuppression therapy, and specific recommendations were elaborated by American Association for the Study of Liver Diseases, European Association for the Study of the Liver and Association for the Study of the Liver^[59,73,74]. Nonetheless, significant questions regarding the optimal antiviral prophylaxis strategy have yet to be addressed.

The effect of prophylactic antiviral therapy on the course of HBV infection in IBD patients undergoing immunosuppressive therapy has not been studied prospectively, and, until now, only a few studies have reported a good efficacy in a short period of follow-up^[65,66]. As a result, the management strategy for these patients remains uncertain.

Lamivudine prophylaxis was suggested on the basis of its well demonstrated efficacy; however, other nucleotides/nucleosides should be preferred, especially if immunosuppressive therapy is scheduled for more than 12 mo, due to their lower propensity to provoke drug resistance. Conversely, HBsAg- HBcAb+ patients (with or without HBsAb+), given their low risk for reactivation, do not require routine antiviral prophylaxis, but only periodic monitoring (about every 3 mo) for the elevation of aspartate aminotransferase/alanine aminotransferase and HBsAg, to prove the re-emergence of HBV-DNA^[72].

Prophylactic therapy seems to be appropriate when biological therapy is scheduled, especially when combined with other immunosuppressive drugs. The role of antiviral drugs other than lamivudine, including entecavir, ad-

efovir and tenofovir, is still unknown, and further studies are needed^{175]}.

To date, there is no prophylaxis available for HCV reactivation. Interferon, which is currently the milestone of antiviral therapy for HCV, is contraindicated in IBD forms that require immunosuppressive therapy. The availability of interferon-free regimens could dramatically change this scenario.

CONCLUSION

The issue in question has increasingly gained interest over the past few years, with the emergence of a number of reports (case reports or case series) on the risk of reactivation of hepatitis in immunosuppressed patients with IBD.

The first cases reported in literature date back to the 1990s and studied onco-hematological patients who demonstrated a fulminant HBV reactivation during or after chemotherapy treatments.

In subsequent years, the development and dissemination of biological immunosuppressive drugs led to a significant increase in the number of reports aimed at reaching other clinical settings (dermatology, rheumatology, gastroenterology, *etc.*).

In particular, the use of anti-TNF α is more frequent in the treatment of steroid-dependent and steroid-refractory UC and CD, as well as in the treatment of perianal fistulizing CD or extraintestinal manifestations associated with IBD (ankylosing spondylitis, pyoderma gangrenosum and uveitis).

There have been a number of published guidelines and reviews on this topic that have collected the available evidence and provided recommendations on prophylactic and therapeutic strategies and methods for monitoring patients at risk.

However, it should be noted that, to date, very few clinical studies have been published, and most of their recommendations have been borrowed from other clinical settings. The published studies are mostly retrospective and based on heterogeneous populations, using different therapeutic and prophylactic regimens to obtain conflicting results.

In particular, the two studies with larger series are those of Loras *et al.*^{60]} and Morisco *et al.*^{65]}. The first group analyzed a population of 25 HBsAg+ and 51 HCV-RNA+ patients. Among HBsAg+ patients, 36% experienced a reactivation of the HBV, and 6 of them developed acute liver failure; however, no reactivation was observed in patients with HBsAg-HBcAb positivity. On the other hand, Morisco *et al.* showed a different result in their study. Only 1/6 HBsAg+ (16%) and 1/4 HBcAb+ isolated (25%) had viral reactivations with mild clinical courses.

The two groups of authors agreed on the low risk of HCV reactivation. The study of Morisco *et al.*^{65]} on the screening procedures for HBV and HCV in patients with IBD resized the frequency and severity of the clinical im-

pact of viral reactivation in patients with IBD receiving immunosuppressive therapy.

Today, there are still some gaps in the knowledge regarding this clinical area. Current evidence supports the assumption that the HBsAg+ patients should receive prophylactic antiviral therapy prior to initiating immunosuppressive therapy. Nevertheless, the best strategy to adopt in HCV+ or in isolated HBcAb+ patients remains unclear. In these cases, the risk of viral reactivation seems to be low, compared to the former scenario.

Thus, the current evidence suggest that it is essential to place an increased emphasis on the completion of prospective studies and to discourage further reviews of the literature until new evidence is available.

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