

Criteria Grid
Best Practices and Interventions for the Prevention and Awareness of Hepatitis C

Best Practice/Intervention:	Gisbert JP. et al. (2011) Review article: prevention and management of hepatitis B and C infection in patients with inflammatory bowel disease. <i>Alimentary Pharmacology & Therapeutics</i> , 33(6):619-633.			
Date of Review:	June 13, 2015			
Reviewer(s):	Christine Hu			
Part A				
Category:	Basic Science <input type="checkbox"/> Clinical Science <input type="checkbox"/> Public Health/Epidemiology <input type="checkbox"/> Social Science <input type="checkbox"/> Programmatic Review <input checked="" type="checkbox"/>			
Best Practice/Intervention:	Focus: Hepatitis C <input checked="" type="checkbox"/> Hepatitis C/HIV <input type="checkbox"/> Other: Hepatitis B, inflammatory bowel disease _____ Level: Group <input checked="" type="checkbox"/> Individual <input type="checkbox"/> Other: _____ Target Population: <u>inflammatory bowel disease patients with HBV/HCV infection</u> Setting: Health care setting/Clinic <input checked="" type="checkbox"/> Home <input type="checkbox"/> Other: _____ Country of Origin: <u>Spain</u> Language: English <input checked="" type="checkbox"/> French <input type="checkbox"/> Other: _____			
Part B				
	YES	NO	N/A	COMMENTS
<i>Is the best practice/intervention a meta-analysis or primary research? Please go to Comments section.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Review article: utilize scientific evidence to determine the relationship between inflammatory bowel disease (IBD) and HBV/HCV infection to provide practical conclusions for clinicians to diagnose and treat patients with IBD
<i>The best practice/intervention shows evidence of "scale up" ability</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>The best practice/intervention shows evidence of transferability</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Conclusions from the review can be transferred to clinical settings

<i>The best practice/intervention shows evidence of adaptation</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>Do the methodology/results described allow the reviewer(s) to assess the generalizability of the results?</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Results are generalized.
	YES	NO	N/A	COMMENTS
<i>Are the best practices/methodology/results described applicable in developed countries?</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	The results can be applied to all countries treating patients with IBD and HBV/HCV infection
<i>Are the best practices/methodology/results described applicable in developing countries?</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>The best practice/intervention has utilized a program evaluation process</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>Consultation and feedback with community has taken place</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	The review article was subject to full peer-review
<i>The best practice/intervention is sensitive to gender issues</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>The best practice/intervention is sensitive to multicultural and marginalized populations</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>The best practice/intervention is easily accessed/available electronically</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Full text available to view at http://onlinelibrary.wiley.com/
<i>Is there evidence of a cost effective analysis? If so, what does the evidence say? Please go to Comments section</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>How is the best practice/intervention funded? Please go to Comments section</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	No funding party
<i>Is the best practice/intervention dependent on external funds?</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

Other relevant criteria:

Review article: prevention and management of hepatitis B and C infection in patients with inflammatory bowel disease

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SUMMARY

Background

Viral hepatitis is a very common infection.

Aim

To review the prevention and management of hepatitis B virus (HBV) and hepatitis C virus (HCV) infection in inflammatory bowel disease (IBD).

Methods

Bibliographical searches were performed in MEDLINE up to September 2010.

Results

The prevalence of both HBV and HCV infection in IBD patients is now similar to that of the general population. All IBD patients should be screened for HBV markers at diagnosis. Liver dysfunction in IBD patients treated with immunosuppressants is more frequent and severe in HBV than in HCV carriers and is associated with combined immunosuppression. In patients receiving anti-TNF drugs, HBV reactivation is common unless anti-viral prophylaxis is administered. HBsAg-positive patients should receive anti-viral prophylaxis before starting immunosuppressants. As interferon might worsen underlying IBD, nucleoside/nucleotide analogues are preferred for anti-viral prophylaxis in patients with HBV (tenofovir/entecavir are preferred to lamivudine). IBD patients should be vaccinated against HBV at diagnosis. The response rate to HBV vaccination is low, mainly in those receiving anti-TNF therapy. The serological response to HBV vaccine should be confirmed, and patients with an inadequate response should receive a second full series of vaccine. Peginterferon (\pm ribavirin) for HCV infection is as effective and safe as in non-IBD patients.

Conclusions

The present manuscript poses a series of questions on the prevention and management of HBV/HCV infection in IBD, and attempts to answer them using scientific evidence in order to provide practical conclusions for the clinician.

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INTRODUCTION

Viral hepatitis is a very common infection: over 350 million people worldwide have chronic hepatitis B virus (HBV) infection and over 250 million people have chronic hepatitis C virus (HCV) infection.¹

In the last 10 years, the treatment of inflammatory bowel disease (IBD), which includes both Crohn's disease (CD) and ulcerative colitis (UC), has been marked by the increasing use of immunosuppressors (mainly azathioprine/mercaptopurine and methotrexate) and by the advent of biological therapies. Increasing evidence in favour of immunosuppressors means that they are being used more often and earlier in the course of the disease.

Many issues concerning the relationship between IBD and HBV/HCV infection remain unresolved. For example, the prevalence of HBV and HCV infection in IBD patients has received little attention and it is still unclear which patients should be screened for HBV/HCV and when. Such questions are particularly relevant, as immunomodulator therapy has a clear impact on the natural history of viral hepatitis, although it is not clear which factors increase the risk of HBV reactivation in IBD patients treated with immunosuppressants. Deciding on the most suitable candidates for anti-viral prophylaxis and timing of this treatment are also matters of debate, as is the type of prophylaxis to be chosen. Although a consensus exists on the need to vaccinate IBD patients against HBV infection, vaccination seems to be underused in clinical practice. Furthermore, the efficacy of HBV vaccination, specifically in IBD patients, and the factors influencing this efficacy are unknown. Several types, doses and schedules of HBV vaccination have been recommended in the general population, and it has been suggested that modified dosing regimens might increase response rates in IBD patients. Whether testing for serological immunity should be systematically performed after HBV vaccination in patients with IBD remains controversial, as does the most suitable cut-off titre for antibodies to hepatitis B surface antigen (anti-HBs). It has been suggested that a second course of HBV vaccination is recommendable in IBD patients whose first vaccination attempt fails, but the effectiveness of this rescue strategy has not been proven. We do not know how long anti-HBs antibody titres remain positive after HBV vaccination and, consequently, whether anti-HBs titres should be periodically monitored and whether booster vaccines should be considered. Finally, issues concerning the efficacy and safety of anti-viral treatment in patients with IBD have not been resolved, and more information

is required on the risk of exacerbation of IBD in patients treated with interferon.

The present manuscript poses a series of questions on the relationship between IBD and HBV/HCV infection and attempts to answer them using scientific evidence to provide practical conclusions for the clinician who diagnoses and treats patients with IBD.

Bibliographical searches were performed in MEDLINE up to September 2010 using the following key words (all fields): ('inflammatory bowel disease' OR 'Crohn's disease' OR 'ulcerative colitis') AND hepatitis.

WHAT IS THE PREVALENCE OF HBV AND HCV INFECTION IN IBD PATIENTS?

Knowledge of the prevalence of HBV and HCV infection in patients with IBD is relevant, because the virus can reactivate under immunosuppressive therapy (see below). However, little information is available on the prevalence of HBV and HCV infection in patients with IBD. In the late 1990s, patients with IBD were considered to be at risk of HCV and HBV infection, probably due to previous surgery or blood transfusions.¹⁻⁵

Prevalence of HBV infection

Some relatively 'old' studies have reported a significantly higher prevalence of HBV infection in IBD patients than in controls. For example, Biancone *et al.*² reported that 11% of IBD patients had antibodies to hepatitis B core protein (anti-HBc), a statistically significantly higher figure than in controls. This high prevalence was related to blood transfusions and surgical procedures, suggesting nosocomial transmission of the virus. In contrast, other studies have reported HBV exposure rates in IBD patients that were similar to those of the general population. REPENTINA 1, a recent large-scale cross-sectional multicentre study of 2076 IBD patients consecutively recruited at 17 Spanish hospitals,⁶ found the prevalence of HBV infection to be lower than that reported in previous studies (less than 1% hepatitis B surface antigen (HBsAg)-positive and less than 10% anti-HBc-positive). However, no differences were found between CD and UC, in contrast with other studies, where the prevalence of HBV markers was higher in CD than in UC.²

Studies evaluating the prevalence of HBV infection in patients with IBD are summarised in Table 1.^{2, 6-9} The weighted mean prevalence of HBsAg-positive infection in the five studies included (total population, 3121 patients) was 1%. The corresponding mean value for anti-HBc-positive infection was 8.1%. When only patients with CD were considered, the mean values for HBsAg and anti-

Table 1 | Studies evaluating the prevalence of hepatitis B virus infection in patients with inflammatory bowel disease (IBD)

Author	Publication year	IBD type	No. of patients	HBsAg (%)	Anti-HBc (%)
Biancone <i>et al.</i> ²	2001	CD	332	2.1	11
Biancone <i>et al.</i> ²	2001	UC	162	0.64	11.5
Esteve <i>et al.</i> ⁷	2004	CD	80	3.7	7.5
Tolentino <i>et al.</i> ⁸	2008	IBD	176	2.3	17
Loras <i>et al.</i> ⁶	2009	CD	1128	0.6	7.1
Loras <i>et al.</i> ⁶	2009	UC	928	0.8	8
Chevaux <i>et al.</i> ⁹	2010	CD	252	0.79	2.8
Chevaux <i>et al.</i> ⁹	2010	UC	63	1.59	1.6

CD, Crohn's disease; UC, ulcerative colitis; HBsAg, hepatitis B surface antigen; anti-HBc, antibodies to hepatitis B core protein.

HBc were 1% and 7.2%, whereas for UC patients the values were 0.8% and 8.1%.

Prevalence of HCV infection

Over the past decade, patients with IBD have been considered at risk for HBV/HCV infection, perhaps due to nosocomial transmission. However, large series such as those reported by Biancone *et al.* in Italy revealed that the prevalence of previous HCV infection (demonstrated by the presence of anti-HCV antibodies) was not significantly higher in CD patients than in controls (7.4% vs. 5.1%), and that it was actually lower in UC patients than in controls.² REPENTINA 1 revealed an anti-HCV-positive rate of 2.3% in CD patients and 1.3% in UC patients.⁶ Therefore, as with HBV infection, prevalence of HCV infection in patients with IBD was concluded to be similar to that of the general reference population and lower than that in previously published series. This fact, in addition to the lack of association with invasive procedures, suggests the existence of adequate preventive measures in centres attending these patients.⁶

Table 2 presents a series of studies evaluating the prevalence of HCV infection in patients with IBD.^{2, 6, 7, 9–11} The weighted mean prevalence of anti-HCV-positive infection for the six studies (3575 patients) was 3.3%. When only patients diagnosed with CD were considered, the mean value for anti-HCV was 3.4%, whereas the respective figure for UC patients was 2.7%.

In summary, more than one decade ago, patients with IBD were considered to be at risk of HBV and HCV

Table 2 | Studies evaluating the prevalence of hepatitis C virus (HCV) infection in patients with inflammatory bowel disease (IBD)

Author	Publication year	IBD type	No. of patients	Anti-HCV (%)
Longo <i>et al.</i> ¹⁰	2000	IBD	117	6
Biancone <i>et al.</i> ²	2001	CD	332	7.4
Biancone <i>et al.</i> ²	2001	UC	162	0.6
Esteve <i>et al.</i> ⁷	2004	CD	80	1.2
Bargiggia <i>et al.</i> ¹¹	2005	CD	302	6.2
Bargiggia <i>et al.</i> ¹¹	2005	UC	211	10.9
Loras <i>et al.</i> ⁶	2009	CD	1128	2.3
Loras <i>et al.</i> ⁶	2009	UC	928	1.3
Chevaux <i>et al.</i> ⁹	2010	CD	252	0.79
Chevaux <i>et al.</i> ⁹	2010	UC	63	1.59

CD, Crohn's disease; UC, ulcerative colitis.

infection. Blood transfusion and surgery were thought to be the routes, thus raising the hypothesis of nosocomial transmission. However, recent epidemiologic surveys have found that prevalence in IBD patients is similar to or even lower than in the general population. At present therefore patients with IBD do not appear to be at risk of hepatitis, probably as a result of safety measures for blood transfusions, improved surgical asepsis and universal anti-HBV vaccination.

WHICH IBD PATIENTS SHOULD BE SCREENED FOR PRIOR HBV/HCV EXPOSURE, AND WHEN?

Traditionally, the results of viral (mainly HBV) serology testing has been thought necessary before patients with IBD can start immunosuppressive therapy.¹² Today, it is generally accepted that all IBD patients should be screened for exposure to HBV. In fact, screening for HBV should be performed at diagnosis of IBD, rather than waiting until initiation of therapy with immunomodulators or tumour necrosis factor- α (TNF) antagonists.^{1, 13–15} This recommendation is based on the potential fatal consequences of HBV reactivation and the availability of safe and effective anti-HBV drugs to prevent reactivation.¹ However, no consensus has been reached for HCV screening prior to starting immunomodulators.¹⁶ As the risk of HCV reactivation under immunosuppressive drugs appears to be very low or non-existent (see below), systematic screening of IBD patients cannot be definitively recommended.

WHAT IS THE IMPACT OF IMMUNOSUPPRESSIVE THERAPY ON THE NATURAL HISTORY OF HBV AND HCV INFECTION? WHICH FACTORS INCREASE THE RISK OF HBV REACTIVATION IN PATIENTS WITH IBD TREATED WITH IMMUNOSUPPRESSANTS?

Effect of immunosuppressants on HBV infection

Reactivation of HBV is an important concern for patients taking immunosuppressants and can manifest in many ways, from a subtle change in serum aminotransferase levels to fulminant hepatic failure and death.¹ 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 up to 50% of patients where concomitant anti-viral therapy is not used.^{17–19} Mortality from fulminant liver failure after reactivation of HBV in patients receiving chemotherapy is reported in 4–60% of cases.²⁰ In this section, the effect of immunosuppressants (corticosteroids, thiopurines and anti-TNF drugs) on HBV infection is reviewed.

Corticosteroids. Fatal viral reactivation has been described mainly in the context of malignant haemato-

logical disease among patients receiving chemotherapy combined with corticosteroids.²¹ In patients with lymphoma, reactivation of HBV replication is more common when chemotherapy regimens include corticosteroids.²² In one report, HBV reactivation in a patient with UC treated with prednisone (plus azathioprine) resulted in fulminant hepatic failure requiring liver transplantation.²³

Thiopurines. A recent study described two cases of hepatic flare (hepatic decompensation with ascites in one case) thought to be caused by treatment of acute CD with systemic corticosteroids and/or azathioprine.²⁴

Anti-TNF drugs. Reactivation of HBV infection related to infliximab has been reported in a number of patients with diseases other than IBD.^{25–30} Table 3 presents a summary of studies reporting reactivation of HBV after infliximab, specifically in patients with IBD (CD in all cases).^{7, 31–38}

Cases of reactivation after treatment with infliximab have been described in occult carriers of HBV who are negative for HBsAg and positive for anti-HBc antibody³⁷ (see occult HBV infection, below). Reactivation of HBV infection in HBsAg carriers occurred as soon as after the

Table 3 | Hepatitis B reactivations after antitumour necrosis factor (infliximab) in patients with Crohn's disease

Author	Year of publication	HBsAg status	Duration of infliximab treatment	Immunomodulator	Lamivudine	Outcome
del Valle Garcia-Sanchez <i>et al.</i> ³¹	2004	+	6 infusions	None	Yes	Recovered
Esteve <i>et al.</i> ⁷	2004	+†	4 infusions	Azathioprine	No	Recovered
Esteve <i>et al.</i> ⁷	2004	+†	3 infusions	Azathioprine	Yes	Died
Ueno <i>et al.</i> ³²	2005	+	1 infusion	None	No	Recovered
Millonig <i>et al.</i> ³³	2006	+†	4 infusions	Azathioprine	Yes	Recovered
Colbert <i>et al.</i> ³⁴	2007	+	24 months	Corticosteroids Azathioprine	Yes	Died
Esteve <i>et al.</i> ³⁵	2007	+	24 months	Azathioprine	Yes*	Recovered
Loras <i>et al.</i> ³⁶	2010	+	-	Azathioprine	Yes*	Recovered
Loras <i>et al.</i> ³⁶	2010	+	-	Azathioprine	Yes	Died
Loras <i>et al.</i> ³⁶	2010	+	-	Corticosteroids Azathioprine	No	Recovered
Madonia <i>et al.</i> ³⁷	2007	+‡	>12 months (6 infusions)	Corticosteroids	Yes	Recovered
Ojiro <i>et al.</i> ³⁸	2008	+	4 infusions	Mercaptopurine	Yes	Recovered

HBsAg, hepatitis B surface antigen.

* The patient was previously receiving lamivudine, which was combined with adefovir dipivoxil.

† Retrospectively found to be HBsAg-positive.

‡ Pre-treatment HBsAg was negative, but became positive.

first infliximab infusion and as late as 2 years after starting infliximab (Table 3), indicating that this complication may develop at any time during therapy with anti-TNF drugs; consequently, systematic clinical and analytical monitoring should be performed indefinitely in patients treated with these drugs.

Almost all cases of HBV reactivation associated with infliximab have occurred in patients receiving concomitant treatment with other immunosuppressors, such as corticosteroids or thiopurines (Table 3), suggesting that more profound immunosuppression may facilitate viral reactivation. Lamivudine was the main agent administered and, although clinical and analytical recovery was achieved in most of the cases, three patients died. There are no case reports of reactivation of HBV with adalimumab or certolizumab pegol; however, as these are newer TNF antagonists, the risk of reactivation would be expected to be a class effect.¹

Reactivation of HBV infection may be severe if prophylaxis is not administered.³⁵ Some years ago, Esteve *et al.*⁷ reported three CD patients with chronic hepatitis B infection treated with infliximab. Two patients experienced reactivation: the infection resolved in one patient and the other patient died. The third patient, who received concomitant lamivudine, experienced no variations in hepatic clinical or biochemical parameters. In a recent review, Shale *et al.*³⁹ found reports of anti-TNF drugs administered to HBV patients (with and without IBD); outcomes ranged from apparent viral clearance to fatal hepatitis. Most of the patients treated with anti-TNF drugs who did not receive concomitant anti-viral therapy had increased viral loads and serum aminotransferase, and many developed clinically apparent hepatic dysfunction.³⁹

In previous studies, treatment with a combination of immunosuppressants was identified as the most consistent factor related to the risk of de novo and/or reactivation of opportunistic infections in IBD.^{40, 41} The largest study assessing outcome of HBV infection in patients with IBD and its relation to immunosuppressive therapy has recently been published (REPENTINA 2).³⁶ The study sample comprised patients with IBD and viral hepatitis from 19 Spanish hospitals. Liver dysfunction was observed in 9 of 25 (36%) HBsAg-positive patients, six of whom developed hepatic failure. Treatment with ≥ 2 immunosuppressants was an independent predictor of reactivation. In other words, most patients without reactivation received only one immunosuppressant for a short period and/or anti-viral prophylaxis.³⁶ REPENTINA 2 shows that no single immunosuppressant seems to

be more involved in the development of liver dysfunction, which is probably a consequence of combined immunosuppression. In addition, it also demonstrates that the risk of reactivation under immunosuppressive treatment is clearly higher than spontaneous reactivation as part of the natural history of the infection. Thus, the risk of reactivation of HBV seems to be related to the magnitude of immunosuppression.

In summary, HBV carriers with IBD who require immunosuppressive therapy (e.g. corticosteroids, methotrexate or azathioprine) or biological agents (e.g. anti-TNF agents) frequently present reactivation of HBV infection. This reactivation can be severe and may even prove fatal.

Effect of immunosuppressants on HCV infection

Corticosteroids. It seems reasonable to assume that corticosteroids used to treat IBD have no detrimental effect on the course of HCV.¹⁶ However, one patient with CD had an acute flare of HCV infection on discontinuing corticosteroids.⁴² Furthermore, available data on recurrence in the graft after liver transplantation suggest that corticosteroids should be tapered slowly to limit the risk of early recurrent HCV hepatitis and the risk of cholestatic fibrosing hepatitis.^{43, 44}

Thiopurines/methotrexate. *In vitro*, azathioprine has anti-viral activity against HCV.⁴⁵ Data from patients undergoing liver transplantation for HCV infection indicate that azathioprine can be used in HCV-infected patients with IBD.¹⁶ A study of a small series of HCV-infected patients with arthropathy showed no detrimental effect of treatment with methotrexate.⁴⁶

Anti-TNF drugs. The case series suggest that anti-TNF therapy has no adverse effects and that it might even improve HCV infection.^{29, 47–56} Some authors⁵⁷ found no significant differences in liver function or viraemia at baseline or during follow-up in HCV-infected patients receiving infliximab or etanercept for rheumatoid arthritis. Finally, etanercept improved virological response to combined interferon- α plus ribavirin in HCV-positive patients.⁵¹ Etanercept is not used to treat IBD, but its apparent lack of side effects in HCV suggests that other TNF-antagonists may also be low risk.^{1, 39}

The largest series assessing the outcome of HCV infection in patients with IBD and its relation to immunosuppressive therapy revealed liver dysfunction in 8 of 51 HCV-infected patients (16%).³⁶ Most were related to corticosteroids alone and in one case to azathioprine.

However, except for one case with simultaneous positive antibodies against HIV (AIDS) and anti-HBc (suggesting occult HBV infection), liver dysfunction related to HCV was very mild.

In summary, the use of immunomodulators (e.g. corticosteroids, azathioprine or methotrexate) in IBD patients with HCV appears to be low risk. The magnitude of the reactivation is clearly lower for HCV than for HBV.^{36, 58} At present, there are no data to suggest that TNF-antagonists are unsafe in IBD patients with HCV.

HOW FREQUENT IS PROGRESSION TO LIVER CIRRHOSIS IN IBD PATIENTS RECEIVING IMMUNOSUPPRESSANTS?

The proportion of IBD patients with liver cirrhosis and the mean time to development of cirrhosis in both HBV-infected and HCV-infected patients are as reported in the non-IBD population, considering the natural history of both infections.³⁶ In this sense, progression to liver cirrhosis seems to be similar to that previously observed in non-immunosuppressed infected patients.^{59, 60} Thus, administration of immunosuppressants, as is common in IBD, does not seem to increase progression to end-stage liver disease. This contrasts with observations in HCV-infected patients who progress to liver cirrhosis (and even hepatocarcinoma) after liver transplantation.^{61–63}

WHO SHOULD RECEIVE ANTI-VIRAL PROPHYLAXIS AND WHEN?

Although data for IBD patients are scarce, prophylaxis has proven beneficial in patients undergoing chemotherapy. Thus, randomised controlled trials have shown the benefit of prophylaxis with lamivudine to prevent reactivation of HBV in this group.^{64–66} One meta-analysis of lamivudine for prophylaxis of HBV reactivation in immunosuppressed patients included 21 studies and showed that this drug reduced mortality.⁶⁷

The American Association for the Study of Liver Disease (AASLD),⁶⁸ the European Association for the Study of the Liver (EASL)⁶⁸ and the European Crohn and Colitis Organization (ECCO)¹⁶ recommend early introduction of nucleoside/nucleotide analogues for all HBsAg-positive patients requiring immunosuppressive therapy. Anti-viral therapy should be administered to those patients who exhibit positive HBsAg titres with or without active viral replication. Prophylaxis should be prescribed irrespective of the number and type of immunosuppressants administered, whether corticosteroids, immunomodulators, or biologics.¹

Hepatitis B virus prophylaxis is currently recommended in HBsAg-positive patients 7 days prior to initiation of chemotherapy. It should be maintained for 6 months to 1 year after completion of chemotherapy, as HBV reactivation may occur after chemotherapy is discontinued.^{1, 18, 69} In IBD patients in particular, it is recommended to start anti-viral prophylaxis 1–3 weeks prior to the introduction of immunosuppressive therapy and continue it for 6 months after withdrawal.^{7, 16, 53}

WHAT IS THE RELEVANCE OF OCCULT HBV INFECTION? SHOULD ANTI-VIRAL PROPHYLAXIS BE ADMINISTERED?

Occult HBV infection is defined as persistence of B virus genomes in HBsAg-negative individuals.⁷⁰ This condition is more frequent (almost 10% in some series⁶) in patients with HBV markers (anti-HBc with or without anti-HBs). Thus, although AASLD guidelines recommend screening for HBsAg and anti-HBs, screening for anti-HBc has also been recommended to detect occult HBV.^{1, 21}

Before prescribing immunosuppressive therapy, the physician must take into account that IBD patients may have a reactivation of occult HBV infection. Reactivation has been repeatedly observed in patients with haematological malignancies treated with chemotherapy.^{71, 72} Consequently, anti-HBc-positive patients should be treated with caution, because they are potential carriers of occult HBV.^{71, 72}

In a Spanish multicentre trial, liver dysfunction was observed in 36% of HBsAg-positive patients.³⁶ On the contrary, no definite HBV reactivations have been found in anti-HBc-positive patients lacking HBsAg.^{9, 36} There is only one report of HBV reactivation in an anti-HBc-positive/HBsAg-negative patient with CD treated with corticosteroids and infliximab.³⁷ Therefore, systematic use of anti-viral prophylaxis in anti-HBc-positive patients lacking HBsAg cannot be recommended.^{25, 36, 73} This approach differs from that recommended for patients undergoing chemotherapy, particularly with rituximab. In these patients, anti-viral prophylaxis is recommended if anti-HBc is detected – even in patients lacking HBsAg – based on reports of severe HBV reactivation in this setting.⁷⁴ In any case, liver function and HBV DNA should be periodically monitored in anti-HBc-positive patients with or without anti-HBs during immunosuppressive therapy as occult HBV carriers are more frequent in this group.^{1, 21}

WHICH ANTI-VIRAL PROPHYLAXIS SHOULD BE CHOSEN FOR IBD PATIENTS?

In chronic HBsAg-positive carriers, anti-viral prophylaxis with nucleotide/nucleoside analogues is recommended before administering immunosuppressive agents.¹⁶ According to specific guidelines for HBV treatment,^{16, 18} patients with high baseline HBV DNA levels (>2000 IU/mL) should continue anti-viral treatment until endpoints applicable to non-immunosuppressed patients are reached.

If immunosuppressive therapy is expected to last more than 1 year, nucleotide/nucleoside analogues with a lower propensity than lamivudine for generating drug-resistant mutations of HBV DNA might be preferred.¹⁶ Lamivudine resistance commonly develops with prolonged use, and has been detected in up to 30% of patients after 1 year and 70% by 5 years. The emergence of resistance has also been associated with reactivation in patients on long-term anti-TNF therapy.^{35, 75, 76} Esteve *et al.*⁷ reported a case of resistance in a patient with CD who had been taking lamivudine prophylaxis for 5 years. This agent may be appropriate for a short course of prophylaxis during chemotherapy, but immunosuppressive medications for IBD may be required indefinitely. Some CD patients, mainly those with a fistulizing pattern, require long-term therapy with biologics to maintain remission. Thus, alternative anti-viral medications for HBV, such as tenofovir or entecavir, are preferred in these cases, as they have the lowest rates of resistance with long-term use.^{1, 12, 69} In this setting, entecavir is preferred to adefovir because of its rapid action and lack of nephrotoxicity. Nevertheless, there has recently been a report of an HBV flare with entecavir in patients with concurrent CD.²⁴ Interferon- α is best avoided for two reasons: first, it can exacerbate CD and, second, it can cause additional bone marrow suppression.¹⁶

WHO SHOULD BE VACCINATED AGAINST HBV INFECTION AND WHEN?

Universal immunisation beginning at birth and other successful HBV vaccination strategies have resulted in a dramatic reduction in HBV transmission in many countries with historically high endemicity.⁷⁷ In patients diagnosed with IBD, the present method for prevention of opportunistic infections rests on vaccinations and on a thorough clinical and laboratory work-up before administration of immunosuppressors and/or biologics.¹²

Patients with IBD are very likely to need immunosuppressive therapy in the course of their disease. Furthermore, response rates to some vaccines, for example HBV

vaccine, are considerably lower in patients receiving immunosuppressive agents or anti-TNF therapy (see below).^{1, 78} Therefore, given the recommendation to vaccinate before starting treatment with immunosuppressive agents, the best time for immunisation is at diagnosis of IBD.^{1, 12–15}

ARE IBD PATIENTS CORRECTLY VACCINATED AGAINST HBV INFECTION IN CLINICAL PRACTICE?

In spite of the aforementioned recommendations and the presence of significant risk factors in IBD patients,¹² vaccines are under-prescribed, indicating that immunisation against selected vaccine-preventable illnesses – including viral hepatitis – is uncommon. Melmed *et al.*¹³ assessed risk of exposure and immunisation status among patients receiving care in an IBD specialty clinic. Patients completed a self-administered, pretested, structured questionnaire during a routine visit for the management of IBD. Their responses indicated that, although 44% of the study population had at least one risk factor for hepatitis B (e.g. blood transfusion or tattoos), only 28% had been vaccinated against HBV infection. In another study, 49% of gastroenterologists had never recommended vaccinations for IBD patients.⁷⁹ Finally, a Spanish cross-sectional multicentre study⁶ detected vaccination against HBV in only 12% of IBD patients.

The most commonly cited reason for non-immunisation in these patients is ‘never being offered the vaccine’ or ‘didn’t know I needed it’.⁷⁸ Consequently, it is necessary to increase awareness of immunisation guidelines among health care providers and their patients.⁷⁸

In summary, the low rates of vaccination put IBD patients at risk of infections (e.g. HBV infection), which might easily be avoided through a more rigorous and standardised vaccination programme.¹⁵ Such an approach could limit the infectious complications associated with immunomodulating and biological therapies, and should be *a priority* for all gastroenterologists.¹⁵ Fortunately, implementation of universal HBV vaccination programmes in developed countries will minimise this risk in the future, as confirmed by the results of vaccination programs in younger patients.

HOW EFFECTIVE IS HBV VACCINATION?

The primary three-dose vaccine series induces protective antibody concentrations in >95% of healthy infants, children and young adults.^{77, 80, 81} A recent review of 181 clinical studies in which 24 277 individuals were immunised with Engerix-B and 8627 with RECOMBIVAX HBVax II⁸⁰ revealed that seroprotection (>10 mIU/mL of anti-HBs

titres) was achieved in 96% and 94% of patients, respectively, using the three-dose schedule (0, 1 and 6 months).

However, immunosuppressive illnesses in general are associated with reduced immunogenicity following vaccination.⁷⁷ Published data suggest that patients with diseases other than CD and UC who received vaccinations while on immunosuppressive therapy may have a suboptimal serological response with waning protective antibody titres after a variety of vaccinations.¹⁴ Such a response has been observed in non-IBD patients treated with long-term immunosuppressive agents.^{82, 83}

The rate of response to vaccines in IBD patients has received little attention. Inflammatory bowel disease patients who received a booster immunisation with tetanus and diphtheria toxoids produced inadequate levels of antibody titres after vaccination.⁸⁴ The response rate to HBV vaccine seems to be quite low, mainly in patients receiving immunosuppressive agents or anti-TNF therapy.⁷⁸ For example, in the study by Melmed *et al.*, only 33% (3/9) of the subgroup of patients who were immunised had detectable anti-HBs antibody titres.¹³ In the study by Vida Perez *et al.*,⁸⁵ where 43% of IBD patients had received immunosuppressive medication before the first vaccine dose, only 36% had adequate levels of anti-HBs antibodies (i.e. >10 mIU/mL). Finally, Chaparro *et al.*⁸⁶ assessed the efficacy of HBV vaccine (double dosage at 0, 1 and 2 months) in 211 patients with IBD, and found that only 60% of patients had adequate anti-HBs antibody levels (defined as >10 mIU/mL). If the cut-off point for adequate immunity was set at >100 mIU/mL (as some guidelines recommend; see below), the efficacy rate was as low as 34%. In summary, the response rate to HBV vaccine seems to be quite low in IBD patients.

WHAT FACTORS AFFECT THE EFFICACY OF HBV VACCINATION IN IBD PATIENTS?

In diseases other than IBD, the efficacy of HBV vaccination is affected by the type and number of immunomodulators given.^{87, 88} For example, some studies have suggested that patients on TNF inhibitors may have a slightly decreased immune response to influenza vaccine.^{89–91}

Specific data for patients with IBD are very scarce. Some authors have evaluated the serological response to influenza vaccine in patients with IBD and observed that those receiving anti-TNF therapy were less likely to be seroprotected.⁹⁰ Others have demonstrated a suboptimal response to pneumococcal vaccination in patients with IBD who are receiving combination therapy with immunosuppressants plus anti-TNF drugs.⁹²

In healthy individuals, several risk factors for nonresponse have been identified, including immunosuppressive disease, smoking, older age, male gender and high body mass index.⁸¹ Only two studies have provided data on the factors affecting efficacy of HBV vaccine in IBD patients. Vida Perez *et al.*⁸⁵ assessed the immune status of 129 IBD patients receiving HBV vaccine (at 0, 1 and 6 months), and the only factor that correlated with failure of the anti-HBs response to the vaccine was older age. However, concomitant use of immunomodulators or biologics did not affect the efficacy of HBV vaccination. The small sample size (only 10 patients were treated with biologics) and the corresponding low statistical power of this study may explain the lack of statistically significant differences. In fact, a tendency towards a lower rate of response to HBV vaccine was found in patients under immunosuppressive treatment (mainly azathioprine). In the study by Chaparro *et al.*⁸⁶ overall, 34% of patients had adequate anti-HBs antibody levels (defined as >100 mIU/mL); however, the response rate was much lower in patients on anti-TNF therapy (10% vs. 40%), although this difference did not reach statistical significance, again probably due to the small sample size. Patients with rheumatoid arthritis treated with adalimumab can be immunised effectively with pneumococcal and influenza vaccines.⁹³

The lack of response to HBV vaccine by IBD patients may be a consequence of associated immunosuppressive/biological treatment rather than of IBD *per se*. For example, the rate of response to HBV vaccine has been reported to be lower in patients with coeliac disease than in healthy individuals.⁹⁴ However, the response to HBV vaccine in coeliac children who were compliant with a gluten-free diet is no different from that of the healthy population.⁹⁵ Thus, coeliac disease may be one of the immune diseases associated with a reduced response to HBV vaccine; however, this lack of response might not be permanent, and a gluten-free diet and compliance with treatment may ameliorate the immune response to the vaccine.⁹⁵ In this respect, Melmed *et al.*⁹² evaluated immunogenicity with the 23-valent pneumococcal polysaccharide vaccine in IBD patients receiving both anti-TNF agents and immunomodulators, IBD patients not receiving any immunosuppressive therapy, and in healthy controls. Inflammatory bowel disease patients who received combination immunosuppressive therapy mounted a less effective immune response than patients with IBD who received non-immunosuppressive therapy and controls, both of which exhibited a similar good response. Overall, the response of IBD patients to HBV

vaccine seems to be quite low, even in those patients not receiving immunosuppressive/biological treatment,^{85, 86} suggesting that IBD *per se* may be partially responsible for the suboptimal serological response to HBV vaccine.

WHICH TYPE, DOSE AND SCHEDULE OF HBV VACCINATION ARE ADVISABLE?

The standard vaccination schedule involves the administration of three doses, usually at 0, 1 and 6 months.^{12, 77, 78} The second dose should be administered 1 month after the first dose; the third dose should be administered at least 2 months after the second dose (and at least 4 months after the first dose).^{81, 96} Longer intervals may increase final anti-HBs titres, but not seroconversion rates.^{77, 81} Accelerated immunisation schedules (for example, at 0, 1 and 2 months) are effective, although anti-HBs titres are lower when intervals between injections are reduced.⁹⁷

If the combined hepatitis A and hepatitis B vaccine (Twinrix, GlaxoSmithKline Biologicals, Rixensart, Belgium) is used, three doses at 0, 1 and 6 months are administered. Modified dosing regimens, including doubling the standard antigen dose, might increase response rates.^{16, 81, 98–100} For example, immunocompromised patients have received Recombivax HB (Merck & Co., Inc., Whitehouse Station, New Jersey, USA) (40 µg/mL) administered in a three-dose schedule or Engerix-B (GlaxoSmithKline Biologicals, Rixensart, Belgium) (2 × 20 µg/mL) administered in a four-dose schedule (at 0, 1, 2 and 6 months).⁹⁶ One recently developed vaccine, which contains a new adjuvant combination (AS04) and was designed for use in patients with renal insufficiency, has been shown to have an improved immunogenicity profile.¹⁰¹

It remains unknown whether the duration of response of vaccine-related immunity is altered in patients with IBD (with or without immunosuppression); therefore, booster doses or modified dosing schedules would be necessary. In this respect, a four-dose schedule (days 0, 7 and 21–30 followed by a booster dose at month 12) could be appropriate.⁹⁶

SHOULD TESTING FOR SEROLOGICAL IMMUNITY BE PERFORMED AFTER HBV VACCINATION?

Although routine serology testing for immunity is not necessary after vaccination of adults, postvaccination testing is recommended for high-risk individuals whose subsequent clinical management depends on knowledge of their immune status, as is the case in immunocompromised persons, including IBD patients.^{18, 77, 81} As the

response rate to HBV vaccination in IBD patients is quite low, testing for serological immunity should be performed 1–2 months after administration of the last dose of the vaccine series to determine the need for revaccination.^{77, 81}

WHICH IS THE BEST CUT-OFF POINT (ANTI-HBS TITRES) FOR DEFINING ADEQUATE IMMUNITY AFTER HBV VACCINATION?

Assessment of the level of vaccine-induced anti-HBs that protects against HBV infection has revealed that all patients who attained a peak antibody response to vaccination of >10 mIU/mL were protected against carriage of HBsAg.¹⁰² According to the World Health Organization, an anti-HBs concentration of ≥10 mIU/mL measured 1–3 months after administration of the last dose of the primary vaccination series is considered a reliable marker of protection against infection.^{9, 77, 80, 81, 97, 102–104} As time passes, anti-HBs titres frequently become undetectable. A number of long-term studies performed in different epidemiological contexts have confirmed that clinical HBV infection rarely occurs among successfully vaccinated individuals even though the anti-HBs concentrations decline to <10 mIU/mL over time. However, among immunocompromised patients who respond to the vaccine, clinically significant HBV infection has been documented in those who do not maintain anti-HBs concentrations of ≥10 mIU/mL. As the persistence of detectable anti-HBs after vaccination depends on the concentration of postvaccination antibodies, some authors have suggested that the concentration of target anti-HBs might be higher for these patients. Based on this evidence, in the United Kingdom, seroprotection against HBV infection was recently redefined at ≥100 mIU/mL.⁷⁷

IS A SECOND COURSE OF HBV VACCINATION ADVISABLE IN IBD PATIENTS IN WHOM A FIRST VACCINATION ATTEMPT FAILS?

Of persons who did not respond to a primary three-dose vaccine series, 25–50% will respond to an additional dose, and 44–100% will respond to a second three-dose course.^{1, 81} Therefore, those patients found to have anti-HBs concentrations <10 mIU/mL after the primary vaccine series should be revaccinated with three additional doses.^{77, 81, 105} Furthermore, increased vaccine doses (e.g. double the standard dose) were shown to enhance revaccination response rates in one study¹⁰⁶ (although not in another¹⁰⁷). Therefore, it may be suggested to either revaccinate with the standard hepatitis B vaccine regimen using twice the standard dose or

administer the combined hepatitis A and B vaccine (Twinrix).¹⁰⁸ However, although among healthy individuals who did not respond to a primary three-dose series with anti-HBs concentrations of >10 mIU/mL, almost all respond to a three-dose revaccination series,¹⁰⁹ this may not be the case in patients with IBD. Thus, in the study by Chaparro *et al.*,⁸⁶ nonresponders to the first three-dose vaccination received a second course of vaccine (with the same three-dose schedule), and the response (>100 mIU/mL anti-HBs titres) to this second vaccination was only 41%.

FOR HOW LONG DO ANTI-HBS ANTIBODY TITRES REMAIN POSITIVE AFTER HBV VACCINATION? SHOULD PERIODIC CONTROLS (E.G. ANNUALLY) BE PERFORMED AND BOOSTER DOSES CONSIDERED?

Even if patients initially form adequate antibody titres after vaccination, these titres may wane and leave patients unknowingly susceptible to infection.^{110, 111} Vaccine-induced anti-HBs titres decline rapidly in the first year and more gradually afterwards.⁸¹ Among young adults who respond to a primary vaccine series with anti-HBs concentrations of ≥ 10 mIU/mL, up to 50% have low or undetectable concentrations (reflecting anti-HBs loss) 10–15 years after vaccination. Even when anti-HBs concentrations decline to <10 mIU/mL, nearly all healthy persons remain protected against HBV infection.⁸¹ Thus, the vaccine-induced immunologic memory is maintained for at least 12 years in non-immunocompromised persons despite the decline in anti-HBs titres.¹⁰⁴

Limited data are available on the duration of immune memory after hepatitis B vaccination in immunocompromised patients. In studies of long-term protection among HIV-infected persons, breakthrough infections occurring after a decline in anti-HBs concentrations to <10 mIU/mL have been transient and asymptomatic.⁸¹ However, among haemodialysis patients who responded to the vaccine, clinically significant HBV infection has been documented in those who did not maintain anti-HBs concentrations >10 mIU/mL.¹¹² Therefore, immunocompromised patients could need annual testing to assess anti-HBs concentrations.⁸¹ For example, for haemodialysis patients, the need for booster doses should be assessed by annual anti-HBs testing. A booster dose should be administered when anti-HBs levels decline to <10 mIU/mL.⁸¹ For other immunocompromised patients, the need for booster doses has not been determined. Thus, annual testing to assess anti-HBs concentrations (and administering booster doses when anti-HBs

levels decline to <10 mIU/mL) should be considered for IBD patients (perhaps only in those under immunosuppressive treatment), although more studies are necessary to establish this recommendation.

WHAT IS THE EFFICACY OF ANTI-VIRAL TREATMENT FOR VIRAL HEPATITIS IN IBD PATIENTS?

Some authors have demonstrated that IBD patients with HCV infection who receive nonpegylated interferon- α monotherapy have a sustained virological response that is similar to that of non-IBD controls.¹¹ The current first-line treatment regimen for HCV infection is peginterferon- α plus ribavirin. Other authors have analysed the efficacy of this combination regimen in CD patients with chronic hepatitis C and have concluded that efficacy is comparable to that reported in patients without CD.^{1, 11, 62}

WHAT IS THE SAFETY PROFILE OF ANTI-VIRAL TREATMENT IN IBD PATIENTS?

No differences in incidence of adverse events have been observed between IBD patients and non-IBD controls treated with interferon- α for HCV infection.^{11, 113} However, Peyrin-Biroulet *et al.*¹¹⁴ reported eight cases of severe pancytopenia in patients receiving azathioprine for IBD and ribavirin plus peginterferon- α for chronic hepatitis C. The authors prospectively monitored azathioprine metabolites in two of these patients and found a dramatic increase in methylated metabolite levels. Similarly, Chaparro *et al.*¹¹⁵ reported a CD patient initially treated with azathioprine and subsequently receiving peginterferon plus ribavirin who presented with pancytopenia. These results suggest that ribavirin can interact with the metabolism of azathioprine, thus increasing the risk of developing myelotoxicity. Taking into account these observations, treatment with ribavirin and purine analogues should be individualised and patients closely monitored.

WHAT IS THE RISK OF EXACERBATION OF IBD WITH INTERFERON?

Crohn's disease is usually characterised by a Th1-type immune response. Crohn's disease flares have been reported in patients taking interferon- α , which is known to stimulate a Th1-type immune response.¹¹⁶ Therefore, this agent is generally not recommended for patients with chronic HBV infection and concomitant CD, because it may exacerbate CD.^{16, 117, 118} Nevertheless, this recommendation remains controversial, as other authors could not confirm the negative effect of inter-

feron- α in patients with CD.^{2, 4, 48, 56} Scherzer *et al.*⁶² analysed the tolerability of interferon- α plus ribavirin in patients with chronic HCV infection and CD, and concluded that gastrointestinal symptoms may be temporarily exacerbated (6 of the 11 CD patients experienced exacerbation of CD-related symptoms). Nevertheless, increased CD activity is easily managed with short-term medical (glucocorticoid) therapy. Therefore, anti-viral therapy with interferon- α plus ribavirin should be given to HCV-infected CD patients to prevent long-term sequelae of chronic hepatitis.⁶²

Several case reports suggest a potential benefit of interferon- α in patients with UC.^{119–122} However, a Cochrane review including three prospective studies of interferon- α in patients with UC concluded that interferon- α was not an effective option for this condition.¹²³ Patients with UC and concomitant HBV or HCV infection could receive interferon- α as the onset of adverse effects is less likely during the course of UC than during that of CD.^{11, 113, 124, 125} However, case reports have observed new-onset UC during interferon- α treatment or exacerbation of existing UC (or IBD with a predominance of UC).^{116, 124–133} In one of these case reports, the administration of sulfasalazine allowed the patient to receive interferon- α again without a flare-up of UC.¹²⁶ This case suggests the possible efficacy of sulfasalazine therapy in patients with UC complicated by administration of interferon- α .

The review by Horn *et al.*¹³⁴ on the treatment of HCV in the setting of IBD allows us to conclude that interferon- α does not appear to worsen the course of established IBD in patients already on maintenance therapy. The idea that HCV can be safely treated in patients with IBD in a suitable clinical context is reinforced by a retrospective study and a case-control study addressing the subject.^{11, 127} Cottone *et al.* retrospectively studied seven UC and seven CD patients who had undergone treatment with interferon- α monotherapy for hepatitis C, or B for at least 6 months.¹²⁷ All of the patients except two had inactive IBD at the beginning of treatment, and only one of these patients had a mild relapse during therapy. The case-control study by Bargiggia *et al.*¹¹ also suggests that interferon- α therapy is safe in patients with chronic hepatitis C and IBD. The authors treated 10 CD patients and 11 UC patients with interferon- α monotherapy. All of the IBD patients were in clinical remission (or had only mildly active disease) prior to initiating interferon- α . No patient had significant worsening of CD activity index during the interferon- α treatment period or during the following 12 months.

In summary, interferon- α is generally safe for patients with chronic hepatitis C and IBD, provided that the latter is in clinical remission. In other words, treatment of hepatitis C does not appear to worsen the course of IBD when the disease is controlled and maintenance therapy instituted.

CONCLUSIONS

(i) Recent studies demonstrate that the prevalence of both HBV infection and HCV infection in IBD patients is now similar to that of the general population. Inflammatory bowel disease patients should no longer be considered a risk group for viral hepatitis.

(ii) All IBD patients should be screened for HBV markers (HBsAg, anti-HBs, anti-HBc) to rule out HBV infection. The best time for screening is at diagnosis.

(iii) Liver dysfunction in IBD patients treated with immunosuppressants is more frequent and severe in HBV carriers than in HCV carriers and is associated with combined immunosuppression.

(iv) In patients receiving anti-TNF drugs, HBV reactivation is common unless anti-viral prophylaxis is administered. Hepatitis B virus reactivations may cause fulminant hepatic failure in patients on immunosuppressive therapy.

(v) Irrespective of the number and type of immunosuppressants administered, all HBsAg-positive patients should receive anti-viral prophylaxis before starting immunosuppressant therapy in order to avoid hepatitis B flare.

(vi) The systematic use of anti-viral prophylaxis in patients with possible occult HBV infection (HBsAg-negative but anti-HBc-positive markers) does not seem to be necessary.

(vii) As interferon therapy might worsen underlying IBD, nucleoside/nucleotide analogues are preferred for anti-viral prophylaxis in patients with HBV.

(viii) Tenofovir and entecavir are preferred to lamivudine as anti-viral prophylaxis of HBV as they have lower rates of resistance in the long term.

(ix) As patients with IBD are very likely to need immunosuppressive therapy in the course of their disease, they should be vaccinated against HBV at diagnosis.

(x) Hepatitis B virus vaccination is under-used in IBD patients in clinical practice. The low percentage of effective vaccinations makes it advisable to intensify HBV vaccination in IBD.

(xi) The response rate to HBV vaccination in IBD patients seems to be quite low, mainly in those already receiving anti-TNF therapy.

(xii) Modified HBV vaccine dosing regimens, including doubling the standard antigen dose, could increase response rates.

(xiii) The serological response to HBV vaccine should be measured after the completion of vaccination in IBD patients.

(xiv) An anti-HBs concentration of ≥ 10 mIU/mL measured 1–3 months after administration of the last dose of the vaccination is considered a reliable marker of protection against HBV infection; the advantages of increasing this cut-off to ≥ 100 mIU/mL are still unclear.

(xv) Patients with an inadequate response to the vaccination should receive a second full series (three doses) of HBV vaccine, as a relevant proportion of these patients will finally respond.

(xvi) Periodic (e.g. annual) testing to assess anti-HBs concentrations (and administering booster doses when

anti-HBs levels decline to < 10 mIU/mL) may be considered for IBD patients (perhaps only in those under immunosuppressive treatment).

(xvii) If a patient with IBD requires treatment for HCV, the combination of peginterferon plus ribavirin appears to be as effective as in non-IBD patients.

(xviii) No difference in adverse events has been observed between IBD and non-IBD patients treated with interferon for HCV infection. On the other hand, ribavirin may interact with the metabolism of azathioprine, thus increasing the risk of myelotoxicity.

(xix) Interferon is generally safe in patients with chronic hepatitis C and IBD, provided that the inflammatory bowel condition is in clinical remission.

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