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

Javier P Gisbert, María Chaparro, Maria Esteve

▶ **To cite this version:**

Javier P Gisbert, María Chaparro, Maria Esteve. Review article: Prevention and management of hepatitis B and C infection in patients with inflammatory bowel disease. Alimentary Pharmacology and Therapeutics, 2011, 33 (6), pp.619. 10.1111/j.1365-2036.2010.04570.x . hal-00607702

HAL Id: hal-00607702
https://hal.science/hal-00607702

Submitted on 11 Jul 2011

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Alimentary Pharmacology & Therapeutics

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

Journal:	*Alimentary Pharmacology & Therapeutics*
Manuscript ID:	APT-0967-2010.R1
Wiley - Manuscript type:	Review Article
Date Submitted by the Author:	20-Dec-2010
Complete List of Authors:	Gisbert, Javier; La Princesa University Hospital, Gastroenterology Chaparro, María; University Hospital La Princesa, Gastroenterology and Hepatology Esteve, Maria; Hospital Mutua de Terrassa, Gastroenterology
Keywords:	Inflammatory bowel disease < Disease-based, Immunosuppression < Topics, Large intestine < Organ-based, Viral hepatitis < Hepatology

SCHOLARONE™
Manuscripts

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

SHORT TITLE: IBD and viral hepatitis

AUTHORS: Javier P. Gisbert[1], María Chaparro[1], María Esteve[2]

[1]Department of Gastroenterology, Hospital Universitario de La Princesa, Instituto de Investigación Sanitaria Princesa (IP), and Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Madrid, Spain

[2]Department of Gastroenterology, Hospital Universitari Mútua de Terrassa, Fundació per la Recerca Mútua de Terrassa, Terrassa, Catalonia, Spain

ABBREVIATIONS: antibodies to hepatitis B surface antigen (anti-HBs), antibodies to hepatitis B core protein (anti-HBc), Crohn's disease (CD), hepatitis B surface antigen (HBsAg), hepatitis B virus (HBV), hepatitis C virus (HCV), inflammatory bowel disease (IBD), tumor necrosis factor-α (TNF), ulcerative colitis (UC).

KEY WORDS: Crohn's disease, ulcerative colitis, hepatitis B virus, hepatitis C virus, inflammatory bowel disease, interferon, tumor necrosis factor, vaccine.

CORRESPONDENCE

Javier P. Gisbert, M.D.

Playa de Mojácar 29. Urb. Bonanza

28669 Boadilla del Monte, Madrid. Spain

Tel.: 34-913093911; Fax: 34-914022299

E-mail: gisbert@meditex.es

For Peer Review

ABSTRACT

Aim: To review the relationship between inflammatory bowel disease(IBD) and hepatitis B virus(HBV) and hepatitis C virus(HCV) infection.

Methods: Bibliographical searches were performed in MEDLINE up to September 2010.

Results and **Conclusions**: 1)The prevalence of both HBV and HCV infection in IBD patients is now similar to that of the general population. 2)All IBD patients should be screened for HBV markers at diagnosis. 3)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. 4)In patients receiving anti-TNF drugs, HBV reactivation(which may cause fulminant hepatic failure) is common unless antiviral prophylaxis is administered. 5)HBsAg-positive patients should receive antiviral prophylaxis before starting immunosuppressants. 6)As interferon therapy might worsen underlying IBD, nucleoside/nucleotide analogues are preferred for antiviral prophylaxis in patients with HBV (tenofovir/entecavir are preferred to lamivudine). 7)Patients with IBD should be vaccinated against HBV at diagnosis. 8)The response rate to HBV vaccination seems to be quite low, mainly in those already receiving anti-TNF therapy. 9)The serological response to HBV vaccine should be measured after vaccination. 10)Patients with an inadequate response to the vaccination should receive a second full series of HBV vaccine. 11)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. 12)No difference in adverse events has been observed between IBD and non-IBD patients treated with interferon for HCV infection. 13)Interferon is generally safe in patients with chronic hepatitis C and IBD.

For Peer Review

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 ten 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 favor 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 antiviral 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 titer 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

For Peer Review

attempt fails, but the effectiveness of this rescue strategy has not been proven. We do not know how long anti-HBs antibody titers remain positive after HBV vaccination and, consequently, whether anti-HBs titers should be periodically monitored and whether booster vaccines should be considered. Finally, issues concerning the efficacy and safety of antiviral 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 serious of questions on the relationship between IBD and HBV/HCV infection and attempts to answer them using scientific evidence in order 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 prior surgery or blood transfusions[1-5].

a) 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

For Peer Review

general population. REPENTINA 1, a recent large-scale cross-sectional multicenter study of 2,076 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 summarized in Table 1[2, 6-9]. The weighted mean prevalence of HBsAg-positive infection in the 5 studies included (total population, 3,121 patients) was 1.03%. 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-HBc were 1.04% and 7.2%, while for UC patients the values were 0.82% and 8.1%.

b) 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 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% *versus* 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 centers 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 6 studies (3,575 patients) was 3.25%. When only patients diagnosed with CD were considered, the mean value for anti-HCV was 3.4%, while the respective figure for UC patients was 2.7%.

For Peer Review

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

a) Effect of immunosuppressants on HBV infection

For Peer Review

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 antiviral 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 hematological 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 antibody[37] (see occult HBV infection, below). Reactivation of HBV infection in HBsAg carriers occurred as soon as after the first infliximab infusion and as late as 2 years after starting infliximab (Table 3), indicating that this

For Peer Review

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 antiviral 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, 6 of whom developed hepatic failure. Treatment with ≥ 2 immunosuppressants was an independent predictor of reactivation. In

For Peer Review

other words, most patients without reactivation received only one immunosuppressant for a short period and/or antiviral 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.

b) 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 antiviral 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: Case series suggest that anti-TNF therapy has no adverse effects and that it might even improve HCV infection[29, 47-56]. Some authors[57] found no significant differences in liver function or viremia at baseline or during follow-up in HCV-infected patients receiving infliximab or etanercept for rheumatoid arthritis. Finally, etanercept improved virological response to combined

For Peer Review

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 is 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 antiviral prophylaxis and when?

Although data for IBD patients are scarce, prophylaxis has proven beneficial in patients undergoing chemotherapy. Thus, randomized controlled trials have shown the benefit of

For Peer Review

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. Antiviral therapy should be administered to those patients who exhibit positive HBsAg titers 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].

HBV 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 de Franchis, 2003 #804][1, 18, 69]. In IBD patients in particular, it is recommended to start antiviral 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 antiviral 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 series[6]) 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 hematological malignancies treated with chemotherapy[71-72].

For Peer Review

Consequently, anti-HBc–positive patients should be treated with caution, because they are potential carriers of occult HBV[71-72].

In a Spanish multicenter 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 antiviral 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, antiviral 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, since occult HBV carriers are more frequent in this group[1, 21].

Which antiviral prophylaxis should be chosen for IBD patients?

In chronic HBsAg-positive carriers, antiviral 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 (>2,000 IU/ml) should continue antiviral 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

For Peer Review

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 antiviral 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 2 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 immunization 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 immunization is at diagnosis of IBD[1, 12-15].

Are IBD patients correctly vaccinated against HBV infection in clinical practice?

For Peer Review

In spite of the aforementioned recommendations and the presence of significant risk factors in IBD patients[12], vaccines are underprescribed, indicating that immunization against selected vaccine-preventable illnesses—including viral hepatitis—is uncommon. Melmed et al[13] assessed risk of exposure and immunization 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 1 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 multicenter study[6] detected vaccination against HBV in only 12% of IBD patients.

The most commonly cited reason for non-immunization 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 immunization guidelines among health care providers and their patients[78].

In summary, the low rates of vaccinationputs IBD patients at risk of infections (e.g., HBV infection) that might easily be avoided through a more rigorous and standardized vaccination program[15]. Such an approach could limit the infectious complications associated with immunomodulating and biologic therapies, and should be a priority for all gastroenterologists[15]. Fortunately, implementation of universal HBV vaccination programs in developed countries will minimize this risk in the future, as confirmed by the results of vaccination programs in younger patients.

How effective is HBV vaccination?

The primary 3-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 immunized with Engerix-B and 8,627 with RECOMBIVAX HBVax II[80]

For Peer Review

revealed that seroprotection (> 10 mIU/ml of anti-HBs titers) was achieved in 96% and 94% of patients, respectively, using the 3-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 serologic response with waning protective antibody titers 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. IBD patients who received a booster immunization with tetanus and diphtheria toxoids produced inadequate levels of antibody titers 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 immunized had detectable anti-HBs antibody titers[13]. In the study by Vida 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].

For Peer Review

Specific data for patients with IBD are very scarce. Some authors have evaluated the serologic 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 non-response have been identified, including immunosuppressive disease, smoking, older age, male sex, and high body mass index[81]. Only two studies have provided data on the factors affecting efficacy of HBV vaccine in IBD patients. Vida et al[85] assessed the immune status of 129 IBD patients receiving HBV vaccine (at 0, 1, and 6 months), and the only factor which 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 ten 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 toward 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 immunized effectively with pneumococcal and influenza vaccines[93] .

The lack of response to HBV vaccine by IBD patients may be a consequence of associated immunosuppressive/biologic 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 celiac disease than in healthy individuals[94]. However, the response to HBV vaccine in celiac children who were compliant with a gluten-free diet is no different from that of the healthy population[95]. Thus, celiac disease may be one of the immune diseases associated with a reduced response to HBV vaccine; however, this lack

For Peer Review

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. IBD 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/biologic treatment[85-86], suggesting that IBD *per se* may be partially responsible for the suboptimal serologic response to HBV vaccine.

Which type, dose, and schedule of HBV vaccination are advisable?

The standard vaccination schedule involves the administration of 3 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 titers, but not seroconversion rates[77, 81]. Accelerated immunization schedules (for example, at 0, 1, and 2 months) are effective, although anti-HBs titers are lower when intervals between injections are reduced[97].

If the combined hepatitis A and hepatitis B vaccine (Twinrix®) is used, 3 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® (40 µg/mL) administered in a 3-dose schedule or Engerix-B® (2 x 20 µg/mL) administered in a 4-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].

For Peer Review

It is 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 4-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, post-vaccination 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 titers) 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 titers 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

For Peer Review

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 post-vaccination antibodies, some authors have suggested that the target anti-HBs concentration 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 3-dose vaccine series, 25-50% will respond to an additional dose, and 44-100% will respond to a second 3-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 3 additional doses[77, 81, 105]. Furthermore, increased vaccine doses (e.g., double the standard dose) were shown to enhance revaccination response rates in one study[106] (althouh not in another[107]). 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 3-dose series with anti-HBs concentrations of > 10 mIU/ml, almost all respond to a 3-dose revaccination series[109], this may not be the case in patients with IBD. Thus, in the study by Chaparro et al[86], non-responders to the first 3-dose vaccination received a second course of vaccine (with the same 3-dose schedule), and the response (> 100 mIU/ml anti-HBs titers) to this second vaccination was only 41%.

For how long do anti-HBs antibody titers remain positive after HBV vaccination? Should periodic controls (e.g., annually) be performed and booster doses considered?

For Peer Review

Even if patients initially form adequate antibody titers after vaccination, these titers may wane and leave patients unknowingly susceptible to infection[110-111]. Vaccine-induced anti-HBs titers 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 titers[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 hemodialysis 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 hemodialysis 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 antiviral treatment for viral hepatitis in IBD patients?

Some authors have demonstrated that IBD patients with HCV infection who receive non-

For Peer Review

pegylated 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 analyzed 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 antiviral 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 individualized and patients closely monitored.

What is the risk of exacerbation of IBD with interferon?

CD is usually characterized by a Th1-type immune response. CD 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

For Peer Review

remains controversial, as other authors could not confirm the negative effect of interferon-α in patients with CD[2, 4, 48, 56]. Scherzer et al[62] analyzed 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, antiviral 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, since 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 six 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 ten

For Peer Review

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

1) 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. IBD patients should no longer be considered a risk group for viral hepatitis.
2) 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.
3) 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.
4) In patients receiving anti-TNF drugs, HBV reactivation is common unless antiviral prophylaxis is administered. HBV reactivations may cause fulminant hepatic failure in patients on immunosuppressive therapy.
5) Irrespective of the number and type of immunosuppressants administered, all HBsAg-positive patients should receive antiviral prophylaxis before starting immunosuppressant therapy in order to avoid hepatitis B flare.
6) The systematic use of antiviral prophylaxis in patients with possible occult HBV

For Peer Review

infection (HBsAg-negative but anti-HBc-positive markers) does not seem to be necessary.

7) As interferon therapy might worsen underlying IBD, nucleoside/nucleotide analogues are preferred for antiviral prophylaxis in patients with HBV.

8) Tenofovir and entecavir are preferred to lamivudine as antiviral prophylaxis of HBV, since they have lower rates of resistance in the long term.

9) 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.

10) HBV vaccination is underused in IBD patients in clinical practice. The low percentage of effective vaccinations makes it advisable to intensify HBV vaccination in IBD.

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

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

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

14) 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.

15) 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.

16) 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).

17) If a patient with IBD requires treatment for HCV, the combination of peginterferon plus

For Peer Review

ribavirin appears to be as effective as in non-IBD patients.

18) 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.

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

For Peer Review

REFERENCES

1. Hou JK, Velayos F, Terrault N, Mahadevan U. Viral hepatitis and inflammatory bowel disease. Inflamm Bowel Dis. 2010 Jun;16(6):925-32.
2. Biancone L, Pavia M, Del Vecchio Blanco G, D'Inca R, Castiglione F, De Nigris F, et al. Hepatitis B and C virus infection in Crohn's disease. Inflamm Bowel Dis. 2001 Nov;7(4):287-94.
3. Forns X, Martinez-Bauer E, Feliu A, Garcia-Retortillo M, Martin M, Gay E, et al. Nosocomial transmission of HCV in the liver unit of a tertiary care center. Hepatology. 2005 Jan;41(1):115-22.
4. Salcedo-Mora X, Mate J, Medina J, Nam Cha SJ, Gisbert JP, Moreno-Otero R. Chronic hepatitis C and Crohn's disease: nosocomial infection treatment with PEG-interferon plus ribavirin. Digestion. 2006;73(4):210-4.
5. Broome U, Glaumann H, Hellers G, Nilsson B, Sorstad J, Hultcrantz R. Liver disease in ulcerative colitis: an epidemiological and follow up study in the county of Stockholm. Gut. 1994 Jan;35(1):84-9.
6. Loras C, Saro C, Gonzalez-Huix F, Minguez M, Merino O, Gisbert JP, et al. Prevalence and factors related to hepatitis B and C in inflammatory bowel disease patients in Spain: a nationwide, multicenter study. Am J Gastroenterol. 2009 Jan;104(1):57-63.
7. Esteve M, Saro C, Gonzalez-Huix F, Suarez F, Forne M, Viver JM. Chronic hepatitis B reactivation following infliximab therapy in Crohn's disease patients: need for primary prophylaxis. Gut. 2004 Sep;53(9):1363-5.
8. Tolentino YF, Fogaca HS, Zaltman C, Ximenes LL, Coelho HS. Hepatitis B virus prevalence and transmission risk factors in inflammatory bowel disease patients at Clementino Fraga Filho university hospital. World J Gastroenterol. 2008 May 28;14(20):3201-6.
9. Chevaux JB, Nani A, Oussalah A, Venard V, Bensenane M, Belle A, et al. Prevalence of hepatitis B and C and risk factors for nonvaccination in inflammatory bowel disease patients in Northeast France. Inflamm Bowel Dis. 2010 Jun;16(6):916-24.
10. Longo F, Hebuterne X, Tran A, Staccini P, Hastier P, Schneider S, et al. [Prevalence of hepatitis C in patients with chronic inflammatory bowel disease in the region of Nice and evaluation of risk factors]. Gastroenterol Clin Biol. 2000 Jan;24(1):77-81.
11. Bargiggia S, Thorburn D, Anderloni A, Ardizzone S, Giorgi A, Bianchi Porro G, et al. Is interferon-alpha therapy safe and effective for patients with chronic hepatitis C and inflammatory bowel disease? A case-control study. Aliment Pharmacol Ther. 2005 Aug 1;22(3):209-15.
12. Viget N, Vernier-Massouille G, Salmon-Ceron D, Yazdanpanah Y, Colombel JF. Opportunistic infections in patients with inflammatory bowel disease: prevention and diagnosis. Gut. 2008 Apr;57(4):549-58.
13. Melmed GY, Ippoliti AF, Papadakis KA, Tran TT, Birt JL, Lee SK, et al. Patients with inflammatory bowel disease are at risk for vaccine-preventable illnesses. Am J Gastroenterol. 2006 Aug;101(8):1834-40.
14. Melmed GY. Vaccination strategies for patients with inflammatory bowel disease on immunomodulators and biologics. Inflamm Bowel Dis. 2009 Sep;15(9):1410-6.
15. Wasan SK, Baker SE, Skolnik PR, Farraye FA. A practical guide to vaccinating the inflammatory bowel disease patient. Am J Gastroenterol. 2010 Jun;105(6):1231-8.
16. Rahier JF, Ben-Horin S, Chowers Y, Conlon C, De Munter P, D'Haens G, et al. European evidence-based Consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. J Crohn Colitis. 2009;3:47-91.
17. Mindikoglu AL, Regev A, Schiff ER. Hepatitis B virus reactivation after cytotoxic chemotherapy: the disease and its prevention. Clin Gastroenterol Hepatol. 2006 Sep;4(9):1076-81.
18. Lok AS, McMahon BJ. Chronic hepatitis B. Hepatology. 2007 Feb;45(2):507-39.
19. Firpi RJ, Nelson DR. Management of viral hepatitis in hematologic malignancies. Blood

For Peer Review

Rev. 2008 May;22(3):117-26.
20. Kohrt HE, Ouyang DL, Keeffe EB. Antiviral prophylaxis for chemotherapy-induced reactivation of chronic hepatitis B virus infection. Clin Liver Dis. 2007 Nov;11(4):965-91, x.
21. Chevaux JB, Bigard MA, Bensenane M, Oussalah A, Jarlot S, Belle A, et al. Inflammatory bowel disease and hepatitis B and C. Gastroenterol Clin Biol. 2009 Dec;33(12):1082-93.
22. Cheng AL, Hsiung CA, Su IJ, Chen PJ, Chang MC, Tsao CJ, et al. Steroid-free chemotherapy decreases risk of hepatitis B virus (HBV) reactivation in HBV-carriers with lymphoma. Hepatology. 2003 Jun;37(6):1320-8.
23. Zeitz J, Mullhaupt B, Fruehauf H, Rogler G, Vavricka SR. Hepatic failure due to hepatitis B reactivation in a patient with ulcerative colitis treated with prednisone. Hepatology. 2009 Aug;50(2):653-4.
24. Sacco R, Bertini M, Bresci G, Romano A, Altomare E, Capria A. Entecavir for hepatitis B virus flare treatment in patients with Crohn's disease. Hepatogastroenterology. 2010 Mar-Apr;57(98):242-5.
25. Yeo W, Chan PK, Zhong S, Ho WM, Steinberg JL, Tam JS, et al. Frequency of hepatitis B virus reactivation in cancer patients undergoing cytotoxic chemotherapy: a prospective study of 626 patients with identification of risk factors. J Med Virol. 2000 Nov;62(3):299-307.
26. Ostuni P, Botsios C, Punzi L, Sfriso P, Todesco S. Hepatitis B reactivation in a chronic hepatitis B surface antigen carrier with rheumatoid arthritis treated with infliximab and low dose methotrexate. Ann Rheum Dis. 2003 Jul;62(7):686-7.
27. Michel M, Duvoux C, Hezode C, Cherqui D. Fulminant hepatitis after infliximab in a patient with hepatitis B virus treated for an adult onset still's disease. J Rheumatol. 2003 Jul;30(7):1624-5.
28. Yeo W, Chan PK, Hui P, Ho WM, Lam KC, Kwan WH, et al. Hepatitis B virus reactivation in breast cancer patients receiving cytotoxic chemotherapy: a prospective study. J Med Virol. 2003 Aug;70(4):553-61.
29. Oniankitan O, Duvoux C, Challine D, Mallat A, Chevalier X, Pawlotsky JM, et al. Infliximab therapy for rheumatic diseases in patients with chronic hepatitis B or C. J Rheumatol. 2004 Jan;31(1):107-9.
30. Wendling D, Auge B, Bettinger D, Lohse A, Le Huede G, Bresson-Hadni S, et al. Reactivation of a latent precore mutant hepatitis B virus related chronic hepatitis during infliximab treatment for severe spondyloarthropathy. Ann Rheum Dis. 2005 May;64(5):788-9.
31. del Valle Garcia-Sanchez M, Gomez-Camacho F, Poyato-Gonzalez A, Iglesias-Flores EM, de Dios-Vega JF, Sancho-Zapatero R. Infliximab therapy in a patient with Crohn's disease and chronic hepatitis B virus infection. Inflamm Bowel Dis. 2004 Sep;10(5):701-2.
32. Ueno Y, Tanaka S, Shimamoto M, Miyanaka Y, Hiyama T, Ito M, et al. Infliximab therapy for Crohn's disease in a patient with chronic hepatitis B. Dig Dis Sci. 2005 Jan;50(1):163-6.
33. Millonig G, Kern M, Ludwiczek O, Nachbaur K, Vogel W. Subfulminant hepatitis B after infliximab in Crohn's disease: need for HBV-screening? World J Gastroenterol. 2006 Feb 14;12(6):974-6.
34. Colbert C, Chavarria A, Berkelhammer C. Fulminant hepatic failure in chronic hepatitis B on withdrawal of corticosteroids, azathioprine and infliximab for Crohn's disease. Inflamm Bowel Dis. 2007 Nov;13(11):1453-4.
35. Esteve M, Loras C, Gonzalez-Huix F. Lamivudine resistance and exacerbation of hepatitis B in infliximab-treated Crohn's disease patient. Inflamm Bowel Dis. 2007 Nov;13(11):1450-1.
36. Loras C, Gisbert JP, Minguez M, Merino O, Bujanda L, Saro C, et al. Liver dysfunction related to hepatitis B and C in patients with inflammatory bowel disease treated with immunosuppressive therapy. Gut. 2010 Jun 24;Jun 24. [Epub ahead of print].
37. Madonia S, Orlando A, Scimeca D, Olivo M, Rossi F, Cottone M. Occult hepatitis B and infliximab-induced HBV reactivation. Inflamm Bowel Dis. 2007 Apr;13(4):508-9.
38. Ojiro K, Naganuma M, Ebinuma H, Kunimoto H, Tada S, Ogata H, et al. Reactivation of

For Peer Review

hepatitis B in a patient with Crohn's disease treated using infliximab. J Gastroenterol. 2008;43(5):397-401.
39. Shale MJ, Seow CH, Coffin CS, Kaplan GG, Panaccione R, Ghosh S. Review article: chronic viral infection in the anti-tumour necrosis factor therapy era in inflammatory bowel disease. Aliment Pharmacol Ther. 2010 Jan;31(1):20-34.
40. Toruner M, Loftus EV, Jr., Harmsen WS, Zinsmeister AR, Orenstein R, Sandborn WJ, et al. Risk factors for opportunistic infections in patients with inflammatory bowel disease. Gastroenterology. 2008 Apr;134(4):929-36.
41. Garcia-Vidal C, Rodriguez-Fernandez S, Teijon S, Esteve M, Rodriguez-Carballeira M, Lacasa JM, et al. Risk factors for opportunistic infections in infliximab-treated patients: the importance of screening in prevention. Eur J Clin Microbiol Infect Dis. 2009 Apr;28(4):331-7.
42. Biancone L, Del Vecchio Blanco G, Pallone F, Castiglione F, Bresci G, Sturniolo G. Immunomodulatory drugs in Crohn's disease patients with hepatitis B or C virus infection. Gastroenterology. 2002 Feb;122(2):593-4.
43. Magy N, Cribier B, Schmitt C, Ellero B, Jaeck D, Boudjema K, et al. Effects of corticosteroids on HCV infection. Int J Immunopharmacol. 1999 Apr;21(4):253-61.
44. Vivarelli M, Burra P, La Barba G, Canova D, Senzolo M, Cucchetti A, et al. Influence of steroids on HCV recurrence after liver transplantation: A prospective study. J Hepatol. 2007 Dec;47(6):793-8.
45. Stangl JR, Carroll KL, Illichmann M, Striker R. Effect of antimetabolite immunosuppressants on Flaviviridae, including hepatitis C virus. Transplantation. 2004 Feb 27;77(4):562-7.
46. Nissen MJ, Fontanges E, Allam Y, Zoulim F, Trepo C, Miossec P. Rheumatological manifestations of hepatitis C: incidence in a rheumatology and non-rheumatology setting and the effect of methotrexate and interferon. Rheumatology (Oxford). 2005 Aug;44(8):1016-20.
47. Campbell S, Ghosh S. Infliximab therapy for Crohn's disease in the presence of chronic hepatitis C infection. Eur J Gastroenterol Hepatol. 2001 Feb;13(2):191-2.
48. Holtmann MH, Galle PR, Neurath MF. Treatment of patients with Crohn's disease and concomitant chronic hepatitis C with a chimeric monoclonal antibody to TNF. Am J Gastroenterol. 2003 Feb;98(2):504-5.
49. Magliocco MA, Gottlieb AB. Etanercept therapy for patients with psoriatic arthritis and concurrent hepatitis C virus infection: report of 3 cases. J Am Acad Dermatol. 2004 Oct;51(4):580-4.
50. Parke FA, Reveille JD. Anti-tumor necrosis factor agents for rheumatoid arthritis in the setting of chronic hepatitis C infection. Arthritis Rheum. 2004 Oct 15;51(5):800-4.
51. Zein NN. Etanercept as an adjuvant to interferon and ribavirin in treatment-naive patients with chronic hepatitis C virus infection: a phase 2 randomized, double-blind, placebo-controlled study. J Hepatol. 2005 Mar;42(3):315-22.
52. Vauloup C, Krzysiek R, Greangeot-Keros L, Wendling D, Goupille P, Brault R, et al. Effects of tumor necrosis factor antagonist treatment on hepatitis C-related immunological abnormalities. Eur Cytokine Netw. 2006 Dec;17(4):290-3.
53. Roux CH, Brocq O, Breuil V, Albert C, Euller-Ziegler L. Safety of anti-TNF-alpha therapy in rheumatoid arthritis and spondylarthropathies with concurrent B or C chronic hepatitis. Rheumatology (Oxford). 2006 Oct;45(10):1294-7.
54. Aslanidis S, Vassiliadis T, Pyrpasopoulou A, Douloumpakas I, Zamboulis C. Inhibition of TNFalpha does not induce viral reactivation in patients with chronic hepatitis C infection: two cases. Clin Rheumatol. 2007 Feb;26(2):261-4.
55. Pitarch G, Sanchez-Carazo JL, Mahiques L, Perez-Ferriols MA, Fortea JM. Treatment of psoriasis with adalimumab. Clin Exp Dermatol. 2007 Jan;32(1):18-22.
56. Abdelmalek MF, Liu C, Valentine JF. Successful treatment of chronic hepatitis C with pegylated interferon, ribavirin, and infliximab in a patient with Crohn's disease. Am J Gastroenterol.

For Peer Review

2007 Jun;102(6):1333-4.
57. Peterson JR, Hsu FC, Simkin PA, Wener MH. Effect of tumour necrosis factor alpha antagonists on serum transaminases and viraemia in patients with rheumatoid arthritis and chronic hepatitis C infection. Ann Rheum Dis. 2003 Nov;62(11):1078-82.
58. Vento S, Cainelli F, Longhi MS. Reactivation of replication of hepatitis B and C viruses after immunosuppressive therapy: an unresolved issue. Lancet Oncol. 2002 Jun;3(6):333-40.
59. Seeff LB. The history of the "natural history" of hepatitis C (1968-2009). Liver Int. 2009 Jan;29 Suppl 1:89-99.
60. McMahon BJ. The natural history of chronic hepatitis B virus infection. Hepatology. 2009 May;49(5 Suppl):S45-55.
61. Iacob S, Cicinnati VR, Hilgard P, Iacob RA, Gheorghe LS, Popescu I, et al. Predictors of graft and patient survival in hepatitis C virus (HCV) recipients: model to predict HCV cirrhosis after liver transplantation. Transplantation. 2007 Jul 15;84(1):56-63.
62. Scherzer TM, Staufer K, Novacek G, Steindl-Munda P, Schumacher S, Hofer H, et al. Efficacy and safety of antiviral therapy in patients with Crohn's disease and chronic hepatitis C. Aliment Pharmacol Ther. 2008 Sep 15;28(6):742-8.
63. Beckebaum S, Sotiropoulos GC, Klein CG, Broelsch CE, Saner F, Paul A, et al. Predictive factors of outcome in patients transplanted for hepatitis B. Transplantation. 2009 Mar 27;87(6):872-81.
64. Jang JW, Choi JY, Bae SH, Yoon SK, Chang UI, Kim CW, et al. A randomized controlled study of preemptive lamivudine in patients receiving transarterial chemo-lipiodolization. Hepatology. 2006 Feb;43(2):233-40.
65. Lau GK, Yiu HH, Fong DY, Cheng HC, Au WY, Lai LS, et al. Early is superior to deferred preemptive lamivudine therapy for hepatitis B patients undergoing chemotherapy. Gastroenterology. 2003 Dec;125(6):1742-9.
66. Hsu C, Hsiung CA, Su IJ, Hwang WS, Wang MC, Lin SF, et al. A revisit of prophylactic lamivudine for chemotherapy-associated hepatitis B reactivation in non-Hodgkin's lymphoma: a randomized trial. Hepatology. 2008 Mar;47(3):844-53.
67. Katz LH, Fraser A, Gafter-Gvili A, Leibovici L, Tur-Kaspa R. Lamivudine prevents reactivation of hepatitis B and reduces mortality in immunosuppressed patients: systematic review and meta-analysis. J Viral Hepat. 2008 Feb;15(2):89-102.
68. European Association For The Study Of The L. EASL Clinical Practice Guidelines: management of chronic hepatitis B. J Hepatol. 2009 Feb;50(2):227-42.
69. Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. Hepatology. 2009 Sep;50(3):661-2.
70. Raimondo G, Allain JP, Brunetto MR, Buendia MA, Chen DS, Colombo M, et al. Statements from the Taormina expert meeting on occult hepatitis B virus infection. J Hepatol. 2008 Oct;49(4):652-7.
71. Iannitto E, Minardi V, Calvaruso G, Mule A, Ammatuna E, Di Trapani R, et al. Hepatitis B virus reactivation and alemtuzumab therapy. Eur J Haematol. 2005 Mar;74(3):254-8.
72. Law JK, Ho JK, Hoskins PJ, Erb SR, Steinbrecher UP, Yoshida EM. Fatal reactivation of hepatitis B post-chemotherapy for lymphoma in a hepatitis B surface antigen-negative, hepatitis B core antibody-positive patient: potential implications for future prophylaxis recommendations. Leuk Lymphoma. 2005 Jul;46(7):1085-9.
73. Lok AS, Liang RH, Chiu EK, Wong KL, Chan TK, Todd D. Reactivation of hepatitis B virus replication in patients receiving cytotoxic therapy. Report of a prospective study. Gastroenterology. 1991 Jan;100(1):182-8.
74. Yeo W, Chan TC, Leung NW, Lam WY, Mo FK, Chu MT, et al. Hepatitis B virus reactivation in lymphoma patients with prior resolved hepatitis B undergoing anticancer therapy with or without rituximab. J Clin Oncol. 2009 Feb 1;27(4):605-11.
75. Liaw YF. Hepatitis flares and hepatitis B e antigen seroconversion: implication in anti-

For Peer Review

hepatitis B virus therapy. J Gastroenterol Hepatol. 2003 Mar;18(3):246-52.
76. Conjeevaram HS, Lok AS. Management of chronic hepatitis B. J Hepatol. 2003;38 Suppl 1:S90-103.
77. Hepatitis B vaccines: WHO position paper--recommendations. Vaccine. 2009 Jan 8;28(3):589-90.
78. Sands BE, Cuffari C, Katz J, Kugathasan S, Onken J, Vitek C, et al. Guidelines for immunizations in patients with inflammatory bowel disease. Inflamm Bowel Dis. 2004 Sep;10(5):677-92.
79. Gupta A, Macrae FA, Gibson PR. Vaccination And Screening For Infections In Patients With Inflammatory Bowel Disease: A Survey Of Australian Gastroenterologists. Intern Med J. 2009 Oct 22.
80. Coates T, Wilson R, Patrick G, Andre F, Watson V. Hepatitis B vaccines: assessment of the seroprotective efficacy of two recombinant DNA vaccines. Clin Ther. 2001 Mar;23(3):392-403.
81. Mast EE, Weinbaum CM, Fiore AE, Alter MJ, Bell BP, Finelli L, et al. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) Part II: immunization of adults. MMWR Recomm Rep. 2006 Dec 8;55(RR-16):1-33; quiz CE1-4.
82. Bruguera M, Cremades M, Salinas R, Costa J, Grau M, Sans J. Impaired response to recombinant hepatitis B vaccine in HIV-infected persons. J Clin Gastroenterol. 1992 Jan;14(1):27-30.
83. Elkayam O, Yaron M, Caspi D. Safety and efficacy of vaccination against hepatitis B in patients with rheumatoid arthritis. Ann Rheum Dis. 2002 Jul;61(7):623-5.
84. Stevens R, Oliver M, Brogan M, Heiserodt J, Targan S. Defective generation of tetanus-specific antibody-producing B cells after in vivo immunization of Crohn's disease and ulcerative colitis patients. Gastroenterology. 1985 Jun;88(6):1860-6.
85. Vida Perez L, Gomez Camacho F, Garcia Sanchez V, Iglesias Flores EM, Castillo Molina L, Cerezo Ruiz A, et al. [Adequate rate of response to hepatitis B virus vaccination in patients with inflammatory bowel disease]. Med Clin (Barc). 2009 Mar 14;132(9):331-5.
86. Chaparro M, Villagrasa JR, Rodríguez Nogueiras A, Gisbert JP. Immune response to hepatitis B vaccination in patients with inflammatory bowel disease. Gastroenterology. 2010;138:S197.
87. Wagner D, Wagenbreth I, Stachan-Kunstyr R, Flik J. Failure of vaccination against hepatitis B with Gen H-B-Vax-D in immunosuppressed heart transplant recipients. Clin Investig. 1992 Jul;70(7):585-7.
88. Worns MA, Teufel A, Kanzler S, Shrestha A, Victor A, Otto G, et al. Incidence of HAV and HBV infections and vaccination rates in patients with autoimmune liver diseases. Am J Gastroenterol. 2008 Jan;103(1):138-46.
89. Mamula P, Markowitz JE, Piccoli DA, Klimov A, Cohen L, Baldassano RN. Immune response to influenza vaccine in pediatric patients with inflammatory bowel disease. Clin Gastroenterol Hepatol. 2007 Jul;5(7):851-6.
90. Lu Y, Jacobson DL, Ashworth LA, Grand RJ, Meyer AL, McNeal MM, et al. Immune response to influenza vaccine in children with inflammatory bowel disease. Am J Gastroenterol. 2009 Feb;104(2):444-53.
91. Gelinck LB, van der Bijl AE, Beyer WE, Visser LG, Huizinga TW, van Hogezand RA, et al. The effect of anti-tumour necrosis factor alpha treatment on the antibody response to influenza vaccination. Ann Rheum Dis. 2008 May;67(5):713-6.
92. Melmed GY, Agarwal N, Frenck RW, Ippoliti AF, Ibanez P, Papadakis KA, et al. Immunosuppression impairs response to pneumococcal polysaccharide vaccination in patients with inflammatory bowel disease. Am J Gastroenterol. Jan;105(1):148-54.
93. Kaine JL, Kivitz AJ, Birbara C, Luo AY. Immune responses following administration of influenza and pneumococcal vaccines to patients with rheumatoid arthritis receiving adalimumab. J

For Peer Review

Rheumatol. 2007 Feb;34(2):272-9.
94. Ahishali E, Boztas G, Akyuz F, Ibrisim D, Poturoglu S, Pinarbasi B, et al. Response to hepatitis B vaccination in patients with celiac disease. Dig Dis Sci. 2008 Aug;53(8):2156-9.
95. Ertem D, Gonen I, Tanidir C, Ugras M, Yildiz A, Pehlivanoglu E, et al. The response to hepatitis B vaccine: does it differ in celiac disease? Eur J Gastroenterol Hepatol. 2010 Jul;22(7):787-93.
96. Recommended adult immunization schedule: United States, 2010. Ann Intern Med. 2010 Jan 5;152(1):36-9.
97. Shouval D. Hepatitis B vaccines. J Hepatol. 2003;39 Suppl 1:S70-6.
98. Choudhury SA, Peters VB. Responses to hepatitis B vaccine boosters in human immunodeficiency virus-infected children. Pediatr Infect Dis J. 1995 Jan;14(1):65-7.
99. Fonseca MO, Pang LW, de Paula Cavalheiro N, Barone AA, Heloisa Lopes M. Randomized trial of recombinant hepatitis B vaccine in HIV-infected adult patients comparing a standard dose to a double dose. Vaccine. 2005 Apr 22;23(22):2902-8.
100. Rey D, Krantz V, Partisani M, Schmitt MP, Meyer P, Libbrecht E, et al. Increasing the number of hepatitis B vaccine injections augments anti-HBs response rate in HIV-infected patients. Effects on HIV-1 viral load. Vaccine. 2000 Jan 18;18(13):1161-5.
101. Tong NK, Beran J, Kee SA, Miguel JL, Sanchez C, Bayas JM, et al. Immunogenicity and safety of an adjuvanted hepatitis B vaccine in pre-hemodialysis and hemodialysis patients. Kidney Int. 2005 Nov;68(5):2298-303.
102. Jack AD, Hall AJ, Maine N, Mendy M, Whittle HC. What level of hepatitis B antibody is protective? J Infect Dis. 1999 Feb;179(2):489-92.
103. John TJ, Cooksley G. Hepatitis B vaccine boosters: is there a clinical need in high endemicity populations? J Gastroenterol Hepatol. 2005 Jan;20(1):5-10.
104. Chen DS. Hepatitis B vaccination: The key towards elimination and eradication of hepatitis B. J Hepatol. 2009 Apr;50(4):805-16.
105. Nye FJ, Kennedy N. Update on vaccination guidelines. Br J Hosp Med. 1997 Apr 2-15;57(7):313-8.
106. Bertino JS, Jr., Tirrell P, Greenberg RN, Keyserling HL, Poland GA, Gump D, et al. A comparative trial of standard or high-dose S subunit recombinant hepatitis B vaccine versus a vaccine containing S subunit, pre-S1, and pre-S2 particles for revaccination of healthy adult nonresponders. J Infect Dis. 1997 Mar;175(3):678-81.
107. Goldwater PN. Randomized, comparative trial of 20 micrograms vs 40 micrograms Engerix B vaccine in hepatitis B vaccine non-responders. Vaccine. 1997 Mar;15(4):353-6.
108. Cardell K, Akerlind B, Sallberg M, Fryden A. Excellent response rate to a double dose of the combined hepatitis A and B vaccine in previous nonresponders to hepatitis B vaccine. J Infect Dis. 2008 Aug 1;198(3):299-304.
109. Tan KL, Goh KT, Oon CJ, Chan SH. Immunogenicity of recombinant yeast-derived hepatitis B vaccine in nonresponders to perinatal immunization. JAMA. 1994 Mar 16;271(11):859-61.
110. Lu Y, Jacobson D, Bousvaros A. Immunizations in patients with inflammatory bowel disease. Inflamm Bowel Dis. 2009 Sep;15(9):1417-23.
111. Hall AJ. Boosters for hepatitis B vaccination? Need for an evidence-based policy. Hepatology. 2010 May;51(5):1485-6.
112. Stevens CE, Alter HJ, Taylor PE, Zang EA, Harley EJ, Szmuness W. Hepatitis B vaccine in patients receiving hemodialysis. Immunogenicity and efficacy. N Engl J Med. 1984 Aug 23;311(8):496-501.
113. Tilg H, Vogelsang H, Ludwiczek O, Lochs H, Kaser A, Colombel JF, et al. A randomised placebo controlled trial of pegylated interferon alpha in active ulcerative colitis. Gut. 2003 Dec;52(12):1728-33.
114. Peyrin-Biroulet L, Cadranel JF, Nousbaum JB, Oussalah A, Seddik M, Canva V, et al.

For Peer Review

Interaction of ribavirin with azathioprine metabolism potentially induces myelosuppression. Aliment Pharmacol Ther. 2008 Oct 15;28(8):984-93.
115. Chaparro M, Trapero-Marugan M, Moreno-Otero R, Gisbert JP. Azathioprine plus ribavirin treatment and pancytopenia. Aliment Pharmacol Ther. 2009 Nov 1;30(9):962-3.
116. Villa F, Rumi MG, Signorelli C, Saibeni S, Del Ninno E, Ferrero Bogetto S, et al. Onset of inflammatory bowel diseases during combined alpha-interferon and ribavirin therapy for chronic hepatitis C: report of two cases. Eur J Gastroenterol Hepatol. 2005 Nov;17(11):1243-5.
117. Khalil A, Lucidarme D, Desurmont P, Hamdan-Khalil R, Filoche B. [Crohn's disease associated with interferon and ribavirin treatment for chronic hepatitis C]. Gastroenterol Clin Biol. 2005 Feb;29(2):193-6.
118. Bongiovanni M, Ranieri R, Ferrero S, Casanova F, Monforte A. Crohn's disease onset in an HIV/hepatitis C virus co-infected woman taking pegylated interferon alpha-2b plus ribavirin. AIDS. 2006 Oct 3;20(15):1989-90.
119. Sumer N, Palabiyikoglu M. Induction of remission by interferon-alpha in patients with chronic active ulcerative colitis. Eur J Gastroenterol Hepatol. 1995 Jul;7(7):597-602.
120. Musch E, Andus T, Malek M. Induction and maintenance of clinical remission by interferon-beta in patients with steroid-refractory active ulcerative colitis-an open long-term pilot trial. Aliment Pharmacol Ther. 2002 Jul;16(7):1233-9.
121. Musch E, Andus T, Kruis W, Raedler A, Spehlmann M, Schreiber S, et al. Interferon-beta-1a for the treatment of steroid-refractory ulcerative colitis: a randomized, double-blind, placebo-controlled trial. Clin Gastroenterol Hepatol. 2005 Jun;3(6):581-6.
122. Miike T, Tahara Y, Yamaguchi Y, Harada T, Abe H, Kusumoto K, et al. [A case study: interferon-beta-induced remission of ulcerative colitis in a patient with type C chronic hepatitis]. Nippon Shokakibyo Gakkai Zasshi. 2008 Sep;105(9):1362-6.
123. Seow CH, Benchimol EI, Griffiths AM, Steinhart AH. Type I interferons for induction of remission in ulcerative colitis. Cochrane Database Syst Rev. 2008(3):CD006790.
124. Legaz Huidobro ML, Artaza Varasa T, Alcantara Torres M, Sanchez Ruano JJ, Lopez Carriches I, Martinez Potenciano JL. [Recombinant alfa-2 interferon treatment of a patient with chronic hepatitis B and ulcerative colitis]. Gastroenterol Hepatol. 1996 Feb;19(2):55-7.
125. De Diego Lorenzo A, Kashoob M, Romero M, Parera A, Duran F, Piqueras B, et al. [Treatment with recombinant interferon alfa-2b of a patient with chronic hepatitis C and concomitant ulcerative colitis]. Rev Esp Enferm Dig. 1997 May;89(5):399-401.
126. Mitoro A, Yoshikawa M, Yamamoto K, Mimura M, Yoshikawa Y, Shiroi A, et al. Exacerbation of ulcerative colitis during alpha-interferon therapy for chronic hepatitis C. Intern Med. 1993 Apr;32(4):327-31.
127. Cottone M, Magliocco A, Trallori G, Brignola C, Vandelli C, Ardizzone S, et al. Clinical course of inflammatory bowel disease during treatment with interferon for associated chronic active hepatitis. Ital J Gastroenterol. 1995 Jan-Feb;27(1):3-4.
128. Mavrogiannis C, Papanikolaou IS, Elefsiniotis IS, Psilopoulos DI, Karameris A, Karvountzis G. Ulcerative colitis associated with interferon treatment for chronic hepatitis C. J Hepatol. 2001 Jun;34(6):964-5.
129. Niki T, Nishida K, Honsako Y, Matsumura Y, Ueno H, Fujimi T, et al. [A case of ulcerative colitis along with characteristic features on computed tomography (CT), developed by the treatment with interferon for chronic hepatitis C]. Nippon Shokakibyo Gakkai Zasshi. 2001 Apr;98(4):399-404.
130. Sprenger R, Sagmeister M, Offner F. Acute ulcerative colitis during successful interferon/ribavirin treatment for chronic hepatitis. Gut. 2005 Mar;54(3):438-9; author reply 9.
131. Watanabe T, Inoue M, Harada K, Homma N, Uchida M, Ogata N, et al. A case of exacerbation of ulcerative colitis induced by combination therapy with PEG-interferon alpha-2b and ribavirin. Gut. 2006 Nov;55(11):1682-3.
132. Tursi A. Rapid onset of ulcerative colitis after treatment with PEG-interferon plus ribavirin

for chronic hepatitis C. Inflamm Bowel Dis. 2007 Sep;13(9):1189-90.
133. Morimoto K, Yamagami H, Hosomi S, Ohira M, Suekane T, Kamata N, et al. Development of pouchitis with combination therapy with peg-interferon alpha-2b and ribavirin for chronic hepatitis C in a patient with ulcerative colitis who underwent pouch surgery. Am J Gastroenterol. 2009 Jun;104(6):1609-10.
134. Horn TL, Reynolds J, de Villiers W, Pena LR. Hepatitis C virus and inflammatory bowel disease. Dig Dis Sci. 2009 Jun;54(6):1171-7.

For Peer Review

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 et al[2]	2001	CD	332	2.1	11
Biancone et al[2]	2001	UC	162	0.64	11.5
Esteve et al[7]	2004	CD	80	3.7	7.5
Tolentino et al[8]	2008	IBD	176	2.3	17
Loras et al[6]	2009	CD	1128	0.6	7.1
Loras et al[6]	2009	UC	928	0.8	8
Chevaux et al[9]	2010	CD	252	0.79	2.8
Chevaux et al[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.

For Peer Review

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 et al[10]	2000	IBD	117	6
Biancone et al[2]	2001	CD	332	7.4
Biancone et al[2]	2001	UC	162	0.6
Esteve et al[7]	2004	CD	80	1.2
Bargiggia et al[11]	2005	CD	302	6.2
Bargiggia et al[11]	2005	UC	211	10.9
Loras et al[6]	2009	CD	1,128	2.3
Loras et al[6]	2009	UC	928	1.3
Chevaux et al[9]	2010	CD	252	0.79
Chevaux et al[9]	2010	UC	63	1.59

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

For Peer Review

Table 3. Hepatitis B reactivations after anti-tumor necrosis factor (infliximab) in patients with Crohn's disease.

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

HBsAg: hepatitis B surface antigen.

¶Retrospectively found to be HBsAg-positive.

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

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

For Peer Review