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Author(s): Elisabetta Degasperi, Flavio Caprioli, Omar El Sherif, David Back, Massimo Colombo and Alessio Aghemo

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REVIEW

Challenges in treating patients with inflammatory bowel disease and concurrent viral hepatitis infection

Elisabetta Degasperi[a], Flavio Caprioli[b,c], Omar El Sherif[d,e], David Back[f], Massimo Colombo[a] and Alessio Aghemo[a]

[a]A.M. and A. Migliavacca Center for Liver Disease, Division of Gastroenterology and Hepatology, Fondazione IRCCS CA' Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, Milan, Italy; [b]Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan, Italy; [c]Gastroenterology and Endoscopy Unit, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milan, Italy; [d]Gastroenterology Specialist Registrar, St. James's Hospital, Dublin, Ireland; [e]Research Fellow, School of Medicine, Trinity College Dublin, Dublin, Ireland; [f]Department of Molecular and Clinical Pharmacology, University of Liverpool, Liverpool, UK

ABSTRACT

Introduction: Inflammatory bowel diseases (IBD) require long-term administration of immunomodulatory treatments to maintain disease remission. Due to the high worldwide prevalence of hepatitis B (HBV) or C (HCV) virus infections, presence of concurrent hepatitis can be a relevant clinical issue to manage when treating IBD.

Areas covered: The paper summarizes epidemiological data about IBD and HBV/HCV infection and reviews current knowledge about the natural history of HBV and HCV in the IBD setting, concentrating on risk of hepatitis reactivation during immunosuppressive treatment. Most updated recommendations for management of HBV and HCV infections in IBD patients are discussed.

Expert commentary: The development of new drugs for IBD with different molecular targets and the availability of potent and efficacious antiviral drugs for HBV and HCV will simplify management of hepatitis infection in IBD patients in the near future.

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1. Introduction

The management of patients with chronic viral hepatitis or inflammatory bowel diseases (IBD) has been revolutionized in the last years by the introduction of highly effective treatments. The availability of potent antivirals against hepatitis B virus (HBV) and hepatitis C virus (HCV), as well as the introduction of anti-TNF biological drugs, has improved patients' survival and quality of life. Although viral hepatitis and IBD do not share any common pathological pathway and thus are usually not clinically associated, it is not uncommon to find patients who are both chronically infected with HBV or HCV and have IBD, given the relatively high prevalence of these diseases. As shown by several studies across Europe, the prevalence of patients with coexisting viral hepatitis and IBD usually follows the epidemiology of viral hepatitis in the single country [1,2]. From a clinical standpoint, the management of these patients is challenging due to many reasons: drugs used in the treatment of IBD may result in liver toxicity, thus leading to worsening of the coexisting liver disease; immunosuppressive regimens used to treat IBD may lead to viral reactivation which can progress to liver failure in selected cases; moreover, drug–drug interactions (DDIs) between therapies administered for viral hepatitis or IBD may lead to reduced response rates or unexpected adverse events. In this review, we will analyze the most recent literature on these topics to determine the optimal management of viral hepatitis in patients with IBD in Europe.

2. Epidemiology of HBV and HCV

Prevalence of chronic Hepatitis B in Europe ranges from 0.4–0.5% reported in Northern Europe and countries such as Spain to 3.4% and 5.6% reported in Greece and Romania, respectively, to more than 8% in the strict European neighborhood like Turkey [3,4]. Eastern countries, including Eastern Europe, Russia, and Eastern Asia represent areas with intermediate–high HBV endemicity, with HBV prevalence ranging from 2% to more than 8% in Southeast Asian countries. Although new incident cases are steadily declining due to the implementation of a vaccination policy for HBV in most European countries, the increase in migration from areas of high endemicity that Europe is witnessing might significantly alter the epidemiology profile of HBV in Europe in the next decade. The impact of migration can already be witnessed in countries with a historically high prevalence, such as Italy, where two different populations of chronically HBV-infected patients exist. The first consists mostly of men in their 50–60s that were infected locally decades ago, and usually present with mild moderate liver disease. The second group is mostly constituted by migrants who are of younger age, are often coinfected with HDV or HIV and have features of advanced disease [5]. This second group of HBV patients is often undiagnosed, or not linked to specialist care.

Chronic infection with HCV is found in 0.1–3.2% of the European population, once again with significant heterogeneity between European countries. There is a north–south gradient with an estimated prevalence in Northern Europe of

CONTACT Alessio Aghemo alessio.aghemo@policlinico.mi.it Division of Gastroenterology and Hepatology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, Milano Via F. Sforza 35, 20122 Milan, Italy

around 0.3% increasing to 1–2% in Italy and Greece. Chronic HCV is also highly prevalent in Eastern Europe (Romania reporting 3.2% prevalence) and in the Southern Italian regions, where HCV prevalence is more than 6–8% [3,6–8]. Most HCV cases in Europe can be traced to two global pandemias: the first one occurred from 1940 to 1970 and is related to iatrogenic transmission of the virus through contaminated blood products, while the second one followed the spreading of intravenous-drug use in the 1970s and 1980s [9]. The local epidemiology of HCV in one country can thus be estimated by understanding which pandemia influenced the spread of HCV locally. In Southern Europe, where most HCV cases were infected due to iatrogenic spread, patients are older and the burden of HCV has already peaked and is now declining due to death for liver or not liver-related causes of the original cohort of patients. In Northern Europe on the other hand where nearly 75% of HCV cases can be found in people who inject drugs (PWID), patients are younger and the burden of the disease is still increasing and is expected to peak in the next 10–15 years [10]. Given that HBV, HCV, and IBD do not share common disease pathways, and since the risk of acquiring viral hepatitis through iatrogenic procedures is now extremely low, there is no specific reason to suspect that patients with IBD should more often be chronically infected with HBV or HCV. Supporting this theory are data gathered throughout Europe that demonstrate that the prevalence of chronic HBV or HCV infection in IBD patients mimics what reported in the general population of the specific country [1,2,11–15]. Studies concerning HBV and HCV prevalence in IBD patients are summarized in Table 1.

Many studies have underlined the low prevalence of anti-HBV vaccination in IBD patients, ranging from 12% reported by a Spanish multicenter study to 23% in a single-center Italian experience [1,14]. This results both from little awareness and implementation of immunization policies by physicians and also from reduced efficacy of anti-HBV vaccination in immunocompromised patients (see paragraph 4). However, the development of nationwide HBV vaccination programs in many European countries is expected to raise prevalence of HBV vaccination in the general population in the near future, starting from younger generations.

2.1. Epidemiology of IBD

In close analogy with other immune-mediated diseases, IBD incidence is characterized by a north–south and a urban–rural gradient [16]; additionally, most epidemiological studies have reported a higher prevalence of IBD in Western with respect to Eastern countries. Even if the reasons underlying these geographical trends have not been elucidated, differences in diet, sun exposure, and intestinal microbiome have been implicated [17]. Notably, of the 5 million people worldwide affected by IBD, it is estimated that 1.5 million reside in the United States and nearly 3 million in Europe [18], where a west–east gradient has been reported. However, these data should be interpreted with caution as they are limited by the paucity of high-quality population-based studies available in Eastern and developing countries. Recent studies estimate an annual ulcerative colitis (UC) incidence ranging from 0 to 19.2 per 100,000 and from 0.6 to 24.3 per 100,000/year in North America and Europe, accounting for a prevalence of 37.5–248.6 per 100,000 and 4.9–505 per 100,000, respectively [19]. Similar incidence rates have been reported for Crohn's disease (CD) (0–20.2 per 100,000/year in North America and 0.3–12.7 per 100,000 in Europe). On the contrary, the recent Asia-Pacific Crohn's and Colitis Epidemiology Study (ACCES), including China, Hong Kong, Indonesia, Sri Lanka, Macau, Malaysia, Singapore, and Thailand, reported an average incidence of IBD in Asia of 1.4 per 100,000 individuals, significantly lower than the incidence in the nearby Australia (24 per 100,000) [20]. A more in-depth analysis of disease subtypes led to the demonstration that UC is more prevalent than CD in Europe and in Asia, while the opposite is true for Australia; in the United States, CD and UC are equally distributed [19]. Only scant data are available regarding IBD diffusion in other countries: in Brazil, an incidence of 4.5 and 3.5 per 100,000 individuals has been reported for UC and CD, respectively [21]; in the Punjab state of Northern India, an incidence of 6 per 100,000 has been reported for UC [22].

As IBD prevalence is due to rise in the next years due to compounding prevalence (i.e. an exponential rise in prevalence due to cumulative addition of incident cases in a chronic disease that has a young age of onset and low mortality), several studies suggest that IBD incidence also is on the rise in both Western and Eastern countries. No clear explanations have been provided for the rising incidence of IBD worldwide, even if it has been hypothesized that it may result from a combination of advances in healthcare infrastructure (e.g. easier and quicker access to endoscopy) and environmental factors. The latter explanation is further corroborated by the significantly increased IBD incidence in migrants with respect to that observed in their countries of origin [23].

Table 1. Prevalence of viral hepatitis in IBD patients.

Study	Year	IBD type	Patients	HBsAg %	Anti-HBc %	Anti-HCV %
Biancone et al. [11] Multicentre, Italy	2001	CD/UC	332/162	2.1/0.64	11/11.5	7.4/0.6
Esteve et al. [12] Multicentre, Spain	2004	CD	80	3.7	7.5	1.2
Tolentino et al. [13] Single-center, Brazil	2008	CD + UC	176	2.3	17	–
Loras et al. [14] REPENTINA-1 Spain	2009	CD/UC	1128/928	0.6/0.8	7.1/8	2.3/1.3
Chevaux et al. [15] Single-center, France	2010	CD/UC	252/63	0.79/1.59	2.8/1.6	0.79/1.59
Weightened prevalence			3121	1%	8.1%	3.3%

3. Clinical challenges: interplay between IBD and viral hepatitis

The natural history of HBV or HCV infection in the setting of IBD is poorly understood and studied, due to the scarcity of prospective data and presence of many confounding factors: indeed, exposure to multiple and sequential immunosuppressive treatments for IBD management could theoretically determine a more rapid progression of HBV or HCV-related liver disease. On the other hand, presence of a immune-mediated disease like IBD was considered a relative contraindication to Interferon (IFN)-based treatment of HBV or HCV in the past, due to the increased risk of IBD exacerbation, so that IBD patients were less likely to receive antiviral treatment for HCV in the IFN-based era, thus providing a potential bias in determining a worse outcome of IBD-HCV patients with respect to the HCV general population. In the HBV setting, administration of nucleoside or nucleotide analogs (NUCs), to treat HBV-related chronic hepatitis or prevent HBV reactivation during immunosuppressive therapy, impairs the possibility to evaluate the natural history of HBV infection in IBD patients.

The largest patient series providing information about long-term outcome of liver disease in IBD patients comes from a Spanish multicenter study (REPENTINA study), including 25 HBsAg-positive and 74 HCV-infected patients with known diagnosis of IBD and available data during a follow-up of more than 20 years: 4 out of 25 HBsAg-positive patients (16%) developed liver cirrhosis after a mean of 13.5 ± 4.2 years from the diagnosis of HBV infection, while the corresponding figures for HCV were 8/74 (10.8%) after a median of 16.7 ± 4.8 years. No association was reported between cirrhosis development and prolonged or combined immunosuppressive treatment [24], suggesting that progression of liver disease in IBD patients seems to be similar to what reported in the general HBV or HCV population and that administration of immunosuppressants does not result in accelerated liver disease progression as reported instead for immunosuppressive therapy in the organ transplantation setting.

It is now well known that immunosuppressive treatment confers an increased risk of viral reactivation in HBV infection: this is due to the fact that humoral and, especially, cellular immune responses are crucial for the control of HBV replication [25]. Indeed, tumor necrosis factor-α (TNF-α) and IFN-γ, targeted by immunosuppressants and anti-TNF drugs, are key cytokines involved in HBV clearance from infected hepatocytes, through elimination of cytosolic HBV replicative intermediates and nuclear covalently close circular DNA (cccDNA). Enhanced viral replication during the administration of immunosuppressive regimens results in hepatitis reactivation after the discontinuation of immunosuppressive drugs, when immune reconstitution occurs and infected hepatocytes are targeted by the immune system. As a consequence, hepatitis reactivation typically occurs after immunosuppressive treatment is withdrawn [26].

Current evidence suggests that risk of HBV reactivation is proportionally linked to the level of immunosuppression achieved. 'Conventional' drugs such as corticosteroids and azathioprine (AZA) seem to provide milder immunosuppressive levels and, consequently, a low risk of HBV reactivation has been reported. However, while an Italian group did not observe any reactivation in four HBsAg-positive patients treated with AZA or steroids across a 1-year follow-up period [11], some HBV reactivations during steroids and AZA treatment are described, resulting in fulminant hepatitis and hepatic failure in few cases [24,27,28]. In the REPENTINA trial, 9 out of 25 (36%) HBsAg-positive IBD patients receiving different immunosuppressive regimens experienced HBV reactivation, defined as a 1.5–2-fold increase in aminotransferase values from baseline and HBV-DNA reappearance or increase >2000 IU/ml. Seven out of these nine cases occurred in patients treated with corticosteroids and/or AZA, most cases during combined administration of corticosteroids + AZA, while only two patients experienced HBV reactivation during steroid monotherapy. Six patients were treated with the NUC Lamivudine to manage HBV reactivation; however, in three patients, liver transplantation was required due to development of hepatic failure. Three patients did not receive antiviral treatment and HBV reactivation was managed by tapering the immunosuppressive treatment. Combined immunosuppressive regimen was confirmed at the multivariate analysis as the strongest risk factor for HBV reactivation (OR 8.75, 95% CI 1.16–65.66) [24].

Reinforcing the concept that more pronounced immunosuppression is associated with higher risk of reactivation is the growing number of case reports of HBV reactivations during treatment with anti-TNF drugs, that are characterized by different mechanism of action with respect to standard immunosuppressants [12,29–34]. Taken together, these case reports account for eight HBV reactivations occurring during Infliximab (IFX)-based treatment: CD was the underlying IBD in all cases, and the vast majority of patients received combined treatment with almost another immunosuppressive drug (corticosteroids and/or AZA). Timing for reactivation ranged from 1 IFX infusion to 24-month treatment course; severity of HBV reactivation varied from mild aminotransferase increase to fulminant hepatitis and two out of eight patients died. Six patients received anti-HBV therapy with Lamivudine during viral reactivation, with four patients successfully recovering following antiviral therapy. In the REPENTINA study, IFX was the anti-TNF involved in three out the nine HBV reactivations reported, always in combination regimens with steroids and/or AZA: two patients were treated with Lamivudine or the second-generation NUC Adefovir, which were not able to prevent liver failure and death in one case. The only patient who did not received anti-HBV treatment recovered after discontinuation of immunosuppressants and surgical bowel resection [24].

Another key factor differentiating the risk of HBV reactivation in the IBD setting from patients receiving immunosuppressants for oncologic diseases is the prolonged treatment duration; while chemotherapy is administered for short and repeated cycles, treatment of IBD patients is prolonged long-term, although the level of immunosuppression achieved is lower than classical chemotherapy. The importance of prolonged treatment duration has been confirmed by a retrospective Korean study, evaluating 134 HBsAg-positive IBD patients treated with different kinds of immunosuppressive treatments (corticosteroids, IFX, and AZA/6-mercaptopurine): liver dysfunction occurred in 23 patients (17.2%), prolonged

(>3 months) immunosuppression representing the strongest risk factor [35].

No cases of HBV reactivation with the other anti-TNF drug Adalimumab (ADA) in IBD patients have been described till now; however, HBV reactivations are reported in two patients receiving ADA as anti-TNF treatment for rheumatological diseases, resulting in severe hepatic failure and death in one case [36–38].

In HBsAg-negative anti-HBc-positive patients, that is, patients with previous HBV contact, risk of HBV reactivation due to immunosuppressive treatment seems negligible. Literature reports only four cases of HBV reactivation in anti-HBc-positive patients receiving anti-TNF treatment, efficiently managed through anti-HBV treatment administration, except for one patient developing severe hepatic failure [38–41]. On the other hand, many case series in the rheumatological setting confirm absence of HBV reactivation in more than 200 HBsAg-negative patients receiving different anti-TNF drugs [42].

Concerning HCV-infected patients, administration of immunosuppressive treatment was historically thought to worsen the outcome of liver disease, this hypothesis being reinforced by the accelerated fibrosis progression in HCV patients receiving immunosuppressants for liver transplantation and by the observation that steroid treatment could increase viral load [43,44]. However, these concepts have not been confirmed in the setting of IBD patients, where immunosuppression does not seem to significantly affect liver disease progression [24]. Conversely, modulation of TNF-α pathways has been claimed even beneficial in HCV patients, as TNF-α is involved in liver inflammation and hepatocyte apoptosis, and upregulation of TNF pathways was thought to affect nonresponse to IFN-based treatments [45,46]. Indeed, a randomized controlled trial in HCV-infected patients, investigating the role of the anti-TNF Etanercept in combination with IFN and Ribavirin for anti-HCV treatment, showed a significant reduction in aminotransferase values and a higher HCV-RNA decline in the Etanercept arm [47].

Few data exist about outcome of immunosuppressive therapy for IBD in HCV patients, however presence of HCV infection does not seem to represent a major concern in treatment of IBD patients: in the REPENTINA study, 8/51 (16%) HCV patients treated for IBD developed a 1.5–2-fold increase in aminotransferase values or a significant increase in HCV viral load, however these alterations were not clinically relevant [24]. Similarly, Morisco and colleagues reported mild elevation of transaminases and viral load in 1 out of 10 HCV patients treated for IBD [41] and two more reports about 4 CD patients treated with IFX showed no significant change in liver function tests and serum HCV-RNA during a maximum of 12 months treatment course [48,49]. Apart from IBD patients, many reports concerning anti-TNF treatment for rheumatologic diseases show no significant safety concern in HCV patients in more than 153 patients [42,50]. Finally, methotrexate and AZA have also been shown safe in HCV-infected patients, both in treating rheumatologic diseases and in liver transplanted patients [51].

4. Treatment of viral hepatitis and hepatitis reactivation

Current guidelines from the European Crohn's and Colitis Organisation (ECCO) recommend testing for HBV and HCV markers before starting immunosuppressive treatment for IBD. Concerning HBV, complete serology is required to determine the patient's virological status: in detail, assessment of HBsAg, anti-HBs, anti-HBc is recommended and, in HBsAg-positive patients, HBeAg, anti-HBe, and HBV-DNA quantification are required. These tests allow to define the HBV profile (active carrier, inactive carrier, or anti-HBc positivity), since this status dictates the need for HBV treatment, prophylaxis, or simple monitoring. In HBV patients with IBD, administration of IFN is not recommended due to the potential risk of IBD exacerbations and, thanks to the availability of safe NUCs, management of HBV infection in IBD patients is performed only with these latter drugs [52].

Active carriers are defined as HBsAg-positive, HBeAg- or anti-HBeAg-positive patients, with persistently or fluctuating elevated aminotransferases and active viral replication (HBV-DNA > 2000 IU/ml): this condition, which is defined chronic hepatitis, is associated with progressive liver disease and requires HBV treatment independently from administration of immunosuppressive therapy for IBD. Third-generation NUCs Entecavir or Tenofovir are the recommended drugs, due to the potent antiviral activity, resulting in rapid viral suppression, and high barrier to resistance [53]. As shown by registration trials and real-life studies, these drugs achieve HBV-DNA negativity in more than 99% patients with none or negligible resistance rates long term [54,55] and, consequently, have optimal profile also to manage long-term immunosuppressive treatments required for IBD. Safety and efficacy of NUCs for treating HBV infection in IBD patients have been confirmed in case series and study cohorts [55]. Treatment duration in active carriers is dictated by the need of treating HBV chronic hepatitis per se, independently from immunosuppressive therapy for IBD; at present, NUCs administration is intended life long, although some studies are concentrating on the possibility to stop NUCs administration after many years of efficient viral suppression or after achievement of HBsAg negativity.

Inactive carriers are defined as HBsAg-positive, anti-HBe-positive patients with persistently normal aminotransferases and HBV-DNA < 2000 IU/ml: these patients have no evidence of progressive liver disease and do not require antiviral treatment in the HBV general population. On the contrary, as discussed above, risk of HBV reactivation in HBsAg-positive IBD patients undergoing immunosuppressive therapy ranges from 20% to more than 30% and requires prophylaxis of HBV reactivation by NUCs administration. Risk of HBV reactivation depends on the type of immunosuppressive agent administered: anti-TNF drugs, integrin inhibitors, and a course of prednisone ≤ 10 mg/day for at least 4 weeks are considered at moderate risk, so that prophylaxis is mandatory [56]. There has been much debate about the possibility of using a less potent NUC like Lamivudine to prevent HBV reactivation in inactive carriers, who typically display low levels of HBV replication and, consequently, could be managed by a less expensive drug than third-generation NUCs Entecavir and Tenofovir. However, the prolonged administration of immunosuppression for IBD advises against using a drug with low barrier to resistance as Lamivudine, as some cases of resistance to Lamivudine prophylaxis are described [33], so that today

third-generation NUCs are the preferred drugs for prophylaxis in HBV inactive carriers [52]. Absence of correct prophylaxis strategies and use of weak drugs like Lamivudine could justify bad outcomes reported by studies concentrating on HBV reactivation in IBD patients in past years. HBV prophylaxis should be carried on for the entire duration of immunosuppressive treatment and prolonged after the discontinuation of immunosuppressants due to the fact that the risk of HBV reactivation is higher when immune reconstitution occurs [26,53,56,57]. There is currently much debate about the recommended duration of HBV prophylaxis after discontinuation of immunosuppressive therapy, as at least 6–12 months have been suggested, depending also on the type of immunosuppressive agent administered [26,56].

To simplify and summarize management of HBsAg-positive patients who need immunosuppressive treatment for concurrent IBD, administration of third-generation NUCs Entecavir or Tenofovir is recommended to treat HBV (active carriers) or as a prophylaxis for HBV reactivation (inactive carriers); the duration depends on HBV status, as active carriers need to be treated life long, whereas prophylaxis in inactive carriers can be discontinued 6–12 months after the cessation of immunosuppressive treatment.

HBsAg-negative, anti-HBc-positive patients efficiently resolved HBV infection and do not display serological viral replication. However, HBV ccDNA can be found in hepatocytes and a profound immunosuppression can result in restarting viral replication and HBsAg serum reappearance, the so-called seroreversion [26]. The highest risk of HBV seroreversion is found in onco-hematologic setting, especially in case of potent CD20 B cell antagonists (Rituximab), so that HBV prophylaxis is required. In IBD patients, as well as in rheumatologic diseases, the level of immunosuppression is lower and only isolated cases of seroreversion are described, so that guidelines recommend only periodical (every 3–4 months) monitoring of HBsAg and HBV-DNA, to early detect potential seroreversion and start HBV treatment promptly. The suggested NUC agents to treat seroreversion are again third-generation NUCs Entecavir and Tenofovir, due to the potent antiviral activity and fast virological suppression. This strategy allows to quickly control HBV replication and should be preferred to Lamivudine administration [26,53,55].

Anti-HBV vaccination is recommended in all IBD patients with negative HBV serology: in patients receiving concurrent treatment with immunosuppressants, the standard schedule for HBV vaccination has been shown ineffective in conferring adequate seroprotection [58]. Importantly, adequate serological response to anti-HBs vaccination has been recently reported in healthy subjects exposed to the α4β7 integrin inhibitor vedolizumab, as to suggest that the gut selectivity of this monoclonal antibody may be associated with reduced immunosuppressive effects following exposure to parenteral vaccines [59]. Nonetheless, an accelerated schedule with double-dose recombinant HBsAg (40 mcg at 0–12 months) has been advocated as the best vaccination strategy for IBD patients: in the REPENTINA-3 multicenter study, administration of accelerated double-dose rHBsAg provided seroprotection (anti-HBs title 10–100 mIU/mL) in 110/254 (43%) IBD patients and effective vaccination (anti-HBs > 100 mIU/mL) in 67/254 (27%) [60]. Another study in 241 IBD patients showed higher efficacy rates, respectively, 59% for seroprotection and 42% for vaccination [61]. Serological response to vaccination should be checked after 1 or 2 months, and revaccination is recommended in patients failing to achieve adequate response after a first vaccine course. As seroprotection loss can occur long term, regular monitoring of anti-HBs titles should be performed yearly or every 2 years, and a unique booster dose is recommended to restore anti-HBs title > 100 mIU/mL, especially in patients undergoing anti-TNF treatment [52].

Given the relative safety of immunosuppressive drugs for IBD in HCV-infected patients, current recommendations do not contraindicate immunomodulators in HCV patients, although the decision should be based on the severity of both IBD and liver disease. Regular monitoring of liver function tests and aminotransferases every 3 months is suggested; no safety data exist about treatment of patients suffering from liver dysfunction with immunomodulators and especially anti-TNF drugs, so that they are currently not recommended in decompensated cirrhosis [52].

Current guidelines on management of HBV or HCV-infected IBD patients receiving immunosuppressive treatment are summarized in Table 2.

Table 2. Recommendations for management of HBV or HCV-infected IBD patients receiving immunosuppressive treatment.

HBV	
Before treatment	All patients should be screened for HBV infection: HBsAg, anti-HBs, anti-HBc In HBsAg+ patients → HBeAg, anti-HBe and HBV-DNA assessment In patients with negative HBV markers → anti-HBV vaccination (rHBsAg 40 mcg 0–12 months) Check serological response by anti-HBs dosing 1 or 2 months after vaccination Monitor anti-HBs title every 2 years
HBV active carriers HBsAg+, HBeAg+/anti-HBe+, ALT↑, HBV-DNA++	Anti-HBV therapy with third-generation NUCs (Etecavir or Tenofovir) Duration dictated by liver disease treatment
HBV inactive carriers HBsAg+, anti-HBe+, normal ALT, HBV-DNA < 2000 IU/ml	Prophylaxis with third-generation NUCs (Entecavir or Tenofovir) To be administered until at least 6–12 months after discontinuation of immunosuppressive treatment
Previous HBV exposure HBsAg−, anti-HBc+, anti-HBs±	Monitor HBsAg and HBV-DNA every 3–4 months Start NUC treatment if evidence of seroreversion
HCV	
Before treatment	All patients should be screened for anti-HCV; in anti-HCV+ → HCV-RNA assessment Administration of immunomodulators should be decided basing on liver disease severity Anti-TNF drugs contraindicated in decompensated cirrhosis
During treatment	Monitor liver tests every 3 months (ALT, ALP, GGT, bilirubin, albumin, platelets

NUC: nucleotide/nucleoside analogs; ALT: aminotransferases; ALP: alkaline phosphatase; GGT: γ-glutamil-transpeptidase

In HCV patients, concurrent IBD represented in the past a relative contraindication to IFN-based treatment due to the risk of IBD exacerbation. This was true especially for CD, where administration of IFN was associated with CD onset in previously asymptomatic patients [62,63] or exacerbations of known CD, although an Austrian study on 11 CD patients receiving PegIFN and Ribavirin treatment demonstrated that, in 6 patients exhibiting CD reactivation, the disease could be efficiently managed by optimizing immunosuppressive treatment with steroids [64]. In addition, antiviral treatment in CD patients showed comparable efficacy with respect to the general HCV population. On the other hand, IFN had been initially claimed as a potential adjuvant treatment to induce UC remission, however a randomized-controlled trial in 60 UC patients failed to confirm this hypothesis, although it demonstrated that PegIFN administration in UC patients did not translate in increased adverse events [65]. A review of existing literature concluded that IFN-based treatment could be feasible in patients with stable IBD remission [66].

This notwithstanding, the recent development of direct-acting antiviral drugs (DAAs) to cure HCV infection paved the way to safely achieve viral eradication in IBD patients. Indeed, the elimination of IFN from the recommended standard of care treatment has allowed to extend eligibility to antiviral therapy also in patients suffering from immune-mediated diseases like IBD [67]. While efficacy of DAAs in registration trials and real-life studies exceeds 95% across nearly all genotypes in the HCV general population, more data are currently needed in special populations like IBD patients, although there is no theoretical reason to suspect a reduced DAAs efficacy in this patient population. Concerning safety, the only topic to address are the potential DDIs between DAAs and immunosuppressive drugs, especially anti-TNF.

5. Drug–drug interactions

A pharmacokinetic drug interaction occurs when one drug (perpetrator) alters the concentrations of a second drug (victim). Pharmacokinetic interactions at the level of drug metabolism represent an important site for DDIs. Cytochrome P450 isoenzymes are responsible for the metabolism of many drugs. In particular, CYP3A is responsible for the oxidative metabolism of more than 40% of the drugs in clinical use [68]. Many DDIs are attributable to CYP450 enzyme inhibition or induction. There are limited pharmacokinetic DDI studies between HCV DAA and drugs used in the treatment of IBD. An understanding of drug disposition for drugs used in the treatment of IBD can guide in predicting potential DDIs in the absence of pharmacokinetic interaction studies. Steroids are frequently used systemically or topically in inducing remission in IBD. Systemic absorption of steroids may occur with topical rectal suppositories or foam enemas, but is rarely complete. Prednisolone, the active metabolite of prednisone is formed in vivo by 11β-hydroxydehydrogenase after oral administration. Prednisolone is subsequently metabolized through a CYP3A4-mediated pathway [69]. Drugs that inhibit CYP3A will result in increased systemic exposure of prednisolone, with an increased risk of steroid-related side effects. Prednisone is also a substrate of P-glycoprotein (P-gp) [70,71].

Azathioprine is the prodrug of 6-mercaptopurine, which is further metabolized to natural purines by inosine monophosphate dehydrogenase (IMPDH) [72]. Methotrexate is a substrate of the OATP1B1 and breast cancer resistance protein (BCRP) drug transporters, and is predominantly eliminated unchanged by the kidneys with minimal metabolism [73,74]. Inhibitors of the OATP1B1 or BCRP drug transporters may therefore increase methotrexate concentrations with potential toxicity.

5.1. Ledipasvir–sofosbuvir

Ledipasvir (90 mg) and sofosbuvir (400 mg) are co-formulated in a fixed dose combination that is administered once daily. Neither sofosbuvir nor ledipasvir are metabolized by CYP450 enzymes. Ledipasvir is primarily excreted in bile as unchanged part drug. Sofosbuvir is a P-gp substrate, and ledipasvir is a weak inhibitor of P-gp and BCRP [75]. Coadministration of ledipasvir–sofosbuvir has not been studied with prednisone, azathioprine, or methotrexate. However, a clinically significant interaction with prednisolone azathioprine/6-mercaptopurine, or methotrexate is unlikely based on their metabolic pathways.

5.2. Simeprevir–sofosbuvir

Simeprevir (an NS4/4A protease inhibitor) is metabolized by CYP3A and is a mild inhibitor of intestinal CYP3A and CYP1A2 [76]. No interaction is expected between simeprevir and azathioprine (6-mercaptopurine) or methotrexate. Coadministration of simeprevir with prednisone may result in increased systemic exposure of prednisolone due to inhibition of intestinal CYP3A4 be simeprevir. While no dose adjustment of prednisone is required, monitoring for steroid side effects is recommended.

5.3. Daclatasvir–sofosbuvir

Daclatsavir (an NS5A inhibitor) is a substrate of CYP3A4 and P-gp, and an inhibitor of OATP1B1, P-gp and BCRP [77]. While coadministration has not been studied, no clinically significant interaction is expected between daclatasvir and azathioprine (6-mercaptopurine) or prednisone. A potential interaction exists between daclatasvir and methotrexate. The administration of daclatasvir in a patient receiving methotrexate may result in increased concentrations of methotrexate due to daclatasvir-mediated inhibition of the OATP1B1 drug transporter. Hematological blood monitoring is required with this combination.

5.4. Ritonavir-boosted paritaprevir, ombitasvir plus dasabuvir (P/r/O + D)

Paritaprevir is metabolized by CYP3A and is given with low-dose ritonavir, a potent CYP3A inhibitor to optimize paritaprevir exposure. This combination has the potential for numerous ritonavir-related DDIs. Ritonavir is a potent hepatic and intestinal CYP3A inhibitor, and also inhibits P-gp and BCRP.

Paritaprevir is an inhibitor of OATP-1B1/1B3, P-gp and BCRP. Dasabuvir is an inhibitor of BCRP and P-gp [78–82].

There is no overlap in the metabolic pathways of P/r/O + D and azathioprine/6-mercaptopurine. Therefore, no drug interactions are expected. Monitoring of hematological blood counts would be prudent if P/r/O + D is administered with methotrexate due to BCRP inhibition by ritanovir, paritaprevir, and dasabuvir. Coadministration of P/r/O + D with prednisone has not been studied. Prednisolone exposure may be increased due to CYP3A4 inhibition by ritonavir. Patients should be monitored for steroid-related side effects.

5.5. Grazoprevir–elbasvir

The Food and Drug Administration (FDA) in the United States has recently approved the combination of grazoprevir and elbasvir for the treatment of HCV [83]. Grazoprevir and elbasvir inhibit BCRP, while elbasvir also inhibits P-gp [84]. Methotrexate levels may be increased in the presence of grazoprevir–elbasvir as a result of BCRP inhibition. Patients should be carefully monitored if this combination is used with methotrexate. No interactions are expected with azathioprine/6-mercaptopurine or prednisone.

5.6. Ribavirin

Ribavirin is frequently administered in combination with HCV DAA in patients with cirrhosis or previous treatment experience to maximize response to therapy, and shorten treatment duration [85]. A significant potential interaction exists with ribavirin and azathioprine (6-mercaptopurine). Ribavirin has an inhibitory effect on IMPDH [86], an important enzyme in the metabolic pathway of 6-mercaptopurine. The coadministration of ribavirin with azathioprine or 6-merpatopurine may result in elevated levels of 6-methylthioinosine monophosphate (6-MTITP) through blockade of IMPDH activity [87]. Elevated levels of 6-MTITP have been shown to be associated with myelotoxicity (neutropenia, thrombocytopenia and/or anemia) in patients treated with azathioprine for IBD [72]. Pancytopenia and bone marrow suppression have been reported in eight patients receiving pegylated IFN, ribavirin concomitantly with azathioprine [87]. The combination of ribavirin with azathioprine is contraindicated in patients with high thiopurine methyltransferase (TPMT) levels, and should also ideally be avoided in patients with normal TPMT activity given the risk of myelotoxicity [87]. This potential interaction exists for up to 2 months after the cessation of ribavirin therapy because of its long half-life.

5.7. Biologics for IBD

Biologics including anti-TNF-α antibodies (e.g. infliximab, adalimumab) and anti-integrins (e.g. vedolizumab) have revolutionized the management of IBD. Infliximab and vedolizumab are given as an intravenous infusion, whereas adalimumab is administered via subcutaneous injection. The elimination pathways for these agents have not been characterized and no drug interaction studies have been performed between HCV DAA and biologic agents for IBD. Clinically significant interactions would not however be expected as the biologics are not substrates of CYP450 and gut transporters.

5.8. Nucleoside analogs for hepatitis B

Nucleoside analogs have an excellent safety profile in patients with hepatitis B, including those with decompensated cirrhosis [88]. However, given the low rate of HBsAg seroconversion seen with these agents, prolonged therapy is frequently required [89]. Lamivudine and entecavir are predominantly excreted unchanged in the urine [90,91]. The kidneys primarily excrete tenofovir DF by both tubular filtration and active tubular secretion [92]. There is a potential for competitive inhibition for active tubular secretion if lamivudine and methotrexate are co-prescribed, which may result in increased serum concentrations of either or both drugs with associated potential toxicity. This competitive inhibition for renal tubular secretion may also arise with tenofovir DF and methotrexate. This combination would require close monitoring of renal function.

Main DDIs between HBV/HCV DAAs and IBD agents are summarized in Table 3.

6. Expert commentary

IBD (CD and UC) are chronic diseases affecting the intestinal tract, characterized also by a systemic involvement due to extraintestinal manifestations. The natural course of IBD typically alternates periods of disease remission and recrudescence with reactivations displaying different degrees of severity, potentially resulting in need for surgical treatment. The long course of the disease, the specific bowel involvement resulting in discomforting symptoms, and the severe exacerbations requiring hospitalization and surgery determine a strong impairment in patients' quality of life, in terms of social, working, and also relational disability.

At present, management of these patients is complicated by a limited knowledge of precise causative and pathophysiological mechanisms, so that current treatment strategy requires administration of immunosuppressing/immunomodulating drugs in order to achieve and maintain disease remission. These drugs require careful and specialist management because they are characterized by side effects both short term (i.e. steroid-induced diabetes) and long term (i.e. increased risk of malignancies), so that periodical monitoring is recommended and, in some cases, treatment is supplied only in hospital settings. In this scenario, patient comorbidities and concomitant diseases have to be carefully considered before starting immunosuppressive treatments: as chronic infection with HBV or HCV affect, respectively, more than 400 and 150 million people worldwide, these liver diseases are likely to interplay with IBD according to local epidemiology in different countries.

Due to the potential risk of hepatitis reactivation during immunosuppressing therapy, current management of IBD patients requires screening for HBV and HCV markers before starting immunosuppressive treatment, in order to determine the patient's virological status and consequently the need for treating chronic hepatitis or administering adequate

Table 3. Specific drug-drug interactions between HBV/HCV DAA and IBD agents.

	Prednisolone	Azathioprine/6-MP	Methotrexate
Sofosbuvir–ledipasvir	No interaction expected	No interaction expected	No interaction expected
Sofosbuvir–simeprevir	Potential for increased prednisolone concentrations due to simeprevir intestinal CYP3A inhibition; monitor for steroid side effects	No interaction expected	No interaction expected
Sofosbuvir–daclatasvir	No interaction expected	No interaction expected	Potential for increased methotrexate concentrations due to daclatasvir inhibition of OATP1B1; hematological monitoring required
Paritaprevir/ritonavir Ombitasvir Dasabuvir	Prednisolone exposure may be increased due to ritonavir CYP3A4 inhibition; monitor for steroid side effects	No interaction expected	Interaction not studied; no interaction expected, but hematological monitoring should be considered
Grazoprevir–elbasvir	No interaction expected	No interaction expected	Methotrexate concentrations may be increased due to BCRP & P-gp inhibition; Careful hematological monitoring is required
Ribavirin	No clear data	May result in elevated levels of 6-MTITP due to IMPDH inhibition with risk of myelotoxicity; coadministration contraindicated in patients with high TMPT levels and should be avoided in patients in normal TMPT levels	No pharmacokinetic interaction; this combination may result in anemia
Tenofovir–DF	No clear data	No interaction expected	Potential for increased serum concentrations of methotrexate and tenofovir due to competitive for active renal tubular secretion; renal monitoring required
Lamivudine	No clear data	No interaction expected	Potential for increased serum concentrations of methotrexate and lamivudine due to competitive for active renal tubular secretion; renal monitoring required

6-MP: 6-mercaptopurine; CYP3A: cytochrome P3A4; OATP1B1: organic anion-transporting polypeptide 1B1; BCRP: breast cancer resistance protein; P-gp: P-glycoprotein; MTITP: methylthioinosine monophosphate; IMPDH: inosine monophosphate dehydrogenase; TPMT: thiopurine methyltransferase

prophylaxis to prevent hepatitis reactivation in the HBV setting. As a consequence, this strategy is actually complex because it presumes good knowledge of different hepatitis serological markers and specialist referral for HBV/HCV treatment administration or monitoring.

However, research in the field of viral hepatitis is pushing very hard and the recent development of new DAAs has paved the way for a true revolution in HCV treatment, due to the high efficacy rates and, most of all, the excellent safety profile allowing to treat patients formerly contraindicated to antiviral therapy in the IFN-based era. This is particularly appealing for IBD patients, as risk for IBD reactivation with IFN excluded many patients from the possibility to receive HCV therapy in the past. If widespread of DAAs will be pursed at the global level, HCV eradication will be feasible in the next decades, so that concurrent HCV infection will no longer represent a clinical problem in IBD management. In the HBV setting, on the other hand, current nucleotide/nucleoside analogs are already efficacious and safe, however they achieve only virological suppression and due to the specific HBV replication cycle, are not able to eradicate the virus (the so-called functional cure). This is the specific research area in the HBV field at the moment, where new compounds are intended to target the cccDNA replication machinery, that is also the driving force of viral reactivation during immunosuppressive treatment. If the functional cure will be achieved, also HBV will not impact IBD clinical management so far. Finally, the most important research area in the near future will be the development of new compounds for IBD therapy with the primary goal of achieving remission in patients failing to respond to currently available treatment options. Another primary goal will be to develop IBD drugs targeting different molecular pathways, in order to provide safer and manageable compounds with reduced need for monitoring and fewer side effects. These goals will be achieved only through a deeper insight in pathophysiological mechanisms of IBD that should be pursued by strong effort in basic research.

7. Conclusions and 5-year view

The current management of patients with chronic HBV or HCV and concomitant IBD requires precise definition of the viral disease status, viral replication levels, and disease stage. Internationally accepted guidelines which have been summarized in this paper provide an adequate tool to manage the risk of HBV reactivation, HBsAg seroconversion, and concomitant chronic HCV infection. In the upcoming years, novel therapeutic strategies will be included into the therapeutic armamentarium for patients with active IBD [93]. Among these, it is presumable that a low risk of HBV or HCV reactivation will be observed following administration of compounds with gut-selective mechanisms of action (e.g. α4β7 integrin inhibitors)

or with negligible systemic absorption, (SMAD7 antisense inhibitors). On the contrary, further data are urgently needed to evaluate hepatic toxicity of a novel generation of immunosuppressive drugs for IBD, including JAK inhibitors and anti-IL12/23 monoclonal antibodies, which could potentially interfere with immunological surveillance of hepatotropic viruses. Similarly, further therapeutic advances are expected to enter the HBV and HCV field. For the treatment of HCV, next-generation DAAs will be optimized versions of currently available drugs, with pan-genotypic activity, optimal pharmacokinetic profile and high genetic barrier to resistance that will allow these drugs to be active also in treatment failures to first- and second-generation DAAs. Although it will be mandatory to asses DDIs with these new compounds, the management of viral hepatitis C in patients with IBD is unlikely to be modified by these DAAs. On the other hand, treatment of HBV will be radically transformed in the next years by drugs that target the immune system as well as antivirals that inhibit different steps of the HBV life cycle including modulation and silencing of ccc-DNA transcription. These drugs could solve the need for active prophylaxis of patients receiving immunosuppressive drugs and thus could play a major role in the management of HBV in patients with IBD.

Key issues

- Prevalence of HBV and HCV infections in IBD patients is the same as the general population, according to the local epidemiology of hepatitis infections.
- IBD prevalence and incidence is on the rise both in Western and Eastern countries.
- In HBV infection, immunosuppressive treatments carry an increased risk of hepatitis reactivation, depending on the patient's serological status (active carrier, inactive carrier or resolved HBV infection).
- HBV active carriers need to be treated for chronic hepatitis with NUC-based therapy, independently from administration of immunosuppressive treatment.
- HBV inactive carriers should receive NUC-based prophylaxis for hepatitis reactivation, to be continued until at least 12 months after cessation of immunosuppressive treatment.
- Patients with markers of previous HBV exposure need to be monitored every 3–4 months in order to detect potential seroreversion.
- Anti-HBV vaccination with double-dose accelerated schedule should be administered to all IBD patients with negative HBV markers before starting immunosuppressive treatment.
- In HCV patients, administration of immunosuppressive treatment should be decided basing on liver disease severity (anti-TNF are contraindicated in decompensated cirrhosis) and periodical monitoring of liver function tests is required.
- Careful check of drug-drug interactions between immunosuppressive regimens and HBV/HCV drugs is required before starting treatment.

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