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REVIEW ARTICLE

Management of hepatitis B virus reactivation due to treatment of COVID-19

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Abstract

The world has made significant progress in developing novel treatments for COVID-19 since the pandemic began. Some treatments target the patient's dysregulated inflammatory response during COVID-19 infection and may cause hepatitis B reactivation (HBVr) in patients with current or past hepatitis B virus (HBV) infection. This review summarizes the risk and management of HBVr due to different treatments of COVID-19 in patients who have current or past HBV infection. Abnormal liver function tests are common during COVID-19 infection. Current evidence suggests that current or past HBV infection is not associated with an increased risk of liver injury and severe disease in COVID-19 patients. Among patients who received high-dose corticosteroids, various immunosuppressive monoclonal antibodies and inhibitors of Janus kinase, the risk of HBVr exists, especially among those without antiviral prophylaxis. Data, however, remain scarce regarding the specific use of immunosuppressive therapies in COVID-19 patients with HBV infection. Some results are mainly extrapolated from patients receiving the same agents in other diseases. HBVr is a potentially life-threatening event following profound immunosuppression by COVID-19 therapies. Future studies should explore the use of immunosuppressive therapies in COVID-19 patients with HBV infection and the impact of antiviral prophylaxis on the risk of HBVr.

Keywords SARS-CoV-2 · COVID-19 · Hepatitis B virus · Reactivation · Immunosuppression · Corticosteroids · Tocilizumab · Tofacitinib · Baricitinib · Sarilumab

Introduction

Coronavirus disease 2019 (COVID-19) is caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which is highly infectious. To date, there have been over 240 million people infected globally resulting in 4.9 million deaths [1]. Consequently, COVID-19 was declared a pandemic by the World Health Organization (WHO) in March 2020. As it is so widespread, many

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patients with COVID-19 also have concomitant chronic diseases. One such disease is chronic hepatitis B infection (CHB), which affects 257 million people worldwide [2]. In addition to those with current hepatitis B virus (HBV) infection (hepatitis B surface antigen [HBsAg]-positive), there are a further two billion people worldwide with past or resolved HBV infection (HBsAg-negative with anti-hepatitis B core antibody [HBc]-positive) [2]. The prevalence of CHB and cumulative number of cases of COVID-19 cases in each world region are displayed in Table 1. The prevalence of CHB in large COVID-19 studies has been reported to range from 0.8 to 6.3% [3–8] in Asia, compared with 0.1% in a large study from the United States (US) [9].

Since the COVID-19 pandemic began, the world has seen rapid developments in therapies which has led to the introduction of multiple effective vaccines. At the same time, the treatment approach to hospitalized adults with COVID-19 has also evolved [10]. These treatments can be divided into two main categories: those directed against the SARS-CoV-2 virus itself and those directed against the patient's dysregulated inflammatory response to the virus. The immunosuppressive treatments in the latter category have the potential to cause hepatitis B reactivation (HBVr) in patients with current or past HBV infection [11]. This occurs because the host immune response is responsible for both control of viral replication and inflammatory liver injury. Attenuation of host immunity against HBV during immunosuppressive treatments can lead to increased HBV replication and hepatocyte expression of HBV antigen [12]. When the immunosuppressive treatment is later withdrawn, the host immune system reconstitutes in the presence of heavily HBV antigen-laden hepatocytes resulting in an enhanced immune response against HBV and subsequent liver injury.

In this review, we summarize the current knowledge of the impact of COVID-19 in patients with current or past HBV infection and evaluate the risk of HBVr with current recommended COVID-19 immunosuppressive treatments. We also make recommendations on antiviral prophylaxis for these patients.

Table 1 Prevalence of CHB and COVID-19 cases by WHO region

WHO Region	Estimated prevalence of CHB (%)†	Number of cumulative COVID-19 cases (millions)‡
Africa	6.1	6
Americas	0.7	92
Eastern Mediterranean	3.3	16
Europe	1.6	73
South-East Asia	2.0	43
Western Pacific	6.2	9
Global	3.5	240

HBV = hepatitis B virus

†Data from WHO Global Hepatitis Report 2015 [2]

‡Data from WHO Weekly Epidemiological Update Oct 2021 [1]

Current recommended treatments for hospitalized COVID-19 patients

Patients with mild (and even moderate) COVID-19 disease are often managed at home in many parts of the world. Hospitalization is usually reserved for patients with severe COVID-19 disease, which is more commonly observed in people aged ≥ 60 years, those living in nursing homes or long-term care facilities, and those with chronic medical conditions [10]. In an analysis of more than 615,000 laboratory-confirmed cases reported in the US between April and July 2021, 6.2% of patients required hospitalization, and 1.1% died [13]. People with reported medical conditions (45.4%) were six times more likely to be hospitalized for COVID-19 disease than those without medical conditions (7.6%) [14].

Hospitalized patients who do not require supplementary oxygen are generally managed with supportive care. Most experts recommend against the use of dexamethasone or other corticosteroids in such patients. If patients require oxygen therapy, remdesivir (an antiviral RNA polymerase inhibitor), dexamethasone, or their combination may be considered [15]. In patients with more severe COVID-19 disease requiring escalating supplemental oxygen or non-invasive ventilation, intravenous (IV) tocilizumab (a humanized monoclonal antibody against the interleukin-6 receptor [IL-6R]) or baricitinib (inhibitor of Janus kinase [JAK]) may be added to dexamethasone, with or without remdesivir [16–18]. Therefore, critically ill patients who require invasive mechanical ventilation or even extracorporeal membrane oxygenation may be given very potent immunosuppressive therapy by combining dexamethasone and IV tocilizumab (or alternatively sarilumab, another monoclonal antibody against IL-6R) [19]. The basis of these recommendations comes from the RECOVERY and REMAP-CAP trials which provide consistent evidence that tocilizumab, when administered with corticosteroids, offers a modest mortality benefit in some patients with COVID-19 who are severely ill, rapidly deteriorating with increasing oxygen needs, and have a significant inflammatory response [17, 19]. If tocilizumab or sarilumab are unavailable or not feasible, tofacitinib (another JAK inhibitor) has been recommended since it has also been shown to reduce death or respiratory failure in hospitalized patients with COVID-19 [20]. Furthermore, JAK inhibitors, particularly baricitinib, have theoretical direct antiviral activity through interference with viral endocytosis, and hence potentially prevent the entry of SARS-CoV-2 into susceptible cells [21].

Impact of COVID-19 infection on patients with CHB

Abnormal liver function tests (hepatocellular, cholestatic or mixed), are commonly observed among patients infected by SARS-CoV-2 [22]. Previous studies suggest that alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevations are observed in about 20% of COVID-19 patients [23–25] with AST levels often higher than ALT during the course of the disease [26]. The cause of this LFT pattern is not fully elucidated but does not appear to be related to muscle breakdown or hepatic ischemia. Elevated gamma-glutamyl transferase (GGT) and total bilirubin are reported in 23% and 1%–18% of patients, respectively, while elevation of alkaline phosphatase (ALP) is less common, occurring in 2%–5% of patients [23–25]. Multiple studies have shown that abnormal liver function tests are associated with a higher risk of progressing to severe COVID-19, including acute respiratory distress syndrome, the need for intensive care unit admission, and mortality [24, 25, 27, 28]. Moreover, the presence of liver cirrhosis is also shown to be associated with higher COVID-19-related mortality [29, 30].

Early studies with small sample sizes reported conflicting results on the impact of HBV infection on COVID-19. A report on 105 COVID-19 patients with CHB showed that liver injury was associated with mortality. In particular, death due to acute-on-chronic liver failure occurred in 4/14 COVID-19 patients with CHB who suffered from liver injury [8]. However, other studies showed no difference in clinical outcomes or even fewer adverse clinical outcomes in COVID-19 patients with CHB, compared to those without CHB [3, 31–33]. Most recently, a study from Hong Kong investigated the risk of COVID-19-related mortality in 353 patients with current and 359 with past HBV infection [4]. This study showed that liver injury, but neither current nor past HBV infection, is associated with COVID-19-related mortality. A study of 267 COVID-19 patients with CHB from the Korean nationwide insurance database also demonstrated no association between HBV infection and severe COVID-19 disease or mortality. Clinical outcomes did not differ between CHB patients with and without HBV antiviral treatment [34]. Data on the long-term outcomes after recovery of COVID-19 patients with CHB remain scarce. Future studies need to explore the impact of HBV antiviral agents on the clinical outcomes of COVID-19 patients with CHB, and the long-term outcome of these patients.

The exact mechanisms underlying liver injury in COVID-19 patients with pre-existing CHB can be multifactorial and hard to delineate. On top of the pre-existing HBV-induced liver disease, some additional pathogeneses of liver injury in COVID-19 patients include direct infection of the liver by SARS-CoV-2, dysregulated host inflammatory response, HBVr, as well as the changes in hemodynamic and oxygen delivery in critically ill patients [23]. Drug-induced liver injury from COVID-19 treatments (*e.g.* remdesivir, favipiravir and tocilizumab) has also been reported [35]. Furthermore, abnormal liver function tests have been linked to a higher SARS-CoV-2 viral load during the early phase of infection, which may suggest direct viral damage to the liver early in the disease [36]. In contrast, the difference in viral load between patients with and without ALT/AST elevation is less obvious in later phases of the infection, which implies the involvement of immune-mediated pathways during viral clearance and/or other indirect pathways and the persistently high viral load in the late-onset liver injury [36, 37]. Moreover, ALT/AST elevation is associated with prolonged viral persistence of SARS-CoV-2 [36].

COVID-19 vaccination can protect CHB patients from severe COVID-19 and associated liver injury. Thus, the Global Hepatology Society, which includes the American Association for the Study of Liver Disease (AASLD), European Association for the Study of the Liver (EASL), Latin American Association for the Study of the Liver (ALEH), and Asian Pacific Association for the Study of the Liver (APASL), strongly recommend that all patients with liver disease (including CHB) discuss COVID-19 vaccination with their health care providers [38].

Impact of COVID-19 treatments on HBVr–Corticosteroids

Data from COVID-19 studies

The systemic corticosteroids used in hospitalized patients with severe COVID-19 disease are usually high-dose (dexamethasone 6 mg daily or equivalent) which increases the risk of HBVr, even if administered just for a few days [39]. Hence, routine testing for HBV serology (HBsAg, anti-HBc, and antibodies to HBsAg [anti-HBs]) is recommended in all individuals prior to commencing COVID-19 immunosuppressive treatments.

A Spanish COVID-19 study investigated 72 patients with current or past HBV infection among whom 41% received high-dose corticosteroids alone or in combination with other immunomodulators [40]. The study reported that 0/3 CHB patients and 0/29 HBsAg-negative, anti-HBc-positive patients who received nucleos(t)ide (NA) prophylaxis while on corticosteroids developed HBVr. One (4.5%) out of 22 HBsAg-negative, anti-HBc-positive patients without NA prophylaxis had detectable HBV DNA (< 10 IU/mL, without HBsAg seroreversion) after receiving corticosteroids. Our study from Hong Kong also reported 0/10 COVID-19 patients with CHB who received dexamethasone or hydrocortisone developed HBVr under NA prophylaxis (Table 2)

[4]. The impact of COVID-19 on patients with past HBV infection is not well elucidated, as only a minority of COVID-19 patients have had anti-HBc checked. Based on our aforementioned study in Hong Kong that described the COVID-19 patients with past HBV infection, there is no evidence that past HBV infection increases the risk of liver injury or mortality [4]. The risk of HBVr in patients with past HBV infection is even more difficult to establish but is generally believed to be low-moderate (< 10%). Nevertheless, there is theoretically still a risk of HBVr if the immunosuppression is profound enough, either because of the COVID-19 therapies or by the COVID-19 disease. Hence a high index of suspicion is warranted and monitoring for HBVr should be performed in these patients.

Data from non-COVID-19 studies

Corticosteroids are the most widely used immunosuppressive agents for a wide spectrum of acute and chronic inflammatory diseases, including rheumatological diseases, other immune-mediated diseases such as inflammatory bowel disease (IBD), respiratory and renal diseases, anaphylaxis, and so on [41]. Short courses of corticosteroids were believed to be safe in CHB patients, even in the presence of disease-modifying anti-rheumatic drugs (DMARDs), yet an increase in serum HBV DNA level was observed in patients who were also exposed to biologic agents [42]. The degree of immunosuppression increases with dose and duration of corticosteroids. A prednisolone 20 mg daily or more (*i.e.* dexamethasone ≥ 3 mg daily) for longer than 2 weeks is considered clinically significant immunosuppression and high risk (> 10%) of HBVr in HBsAg-positive patients. However, this duration of corticosteroids remains arbitrarily defined, as our recent real-world cohort study showed that shorter courses (< 7 days) of high-dose corticosteroids might still increase the risk of HBVr flare [43].

Patients with past HBV infection are at moderate risk (1–10%) of HBVr after corticosteroid therapy with an annual risk of 1.8% [44]. However, high peak daily dose of corticosteroid equivalent to > 40 mg prednisolone such as doses used in COVID-19 (i.e. dexamethasone > 6 mg daily), regardless of duration of therapy, can increase the risk for hepatitis flare by 2–3 times in HBsAg-negative, anti-HBc-positive patients [44].

Impact of COVID-19 treatments on HBVr–Non-corticosteroid drugs

As aforementioned, various immunosuppressive monoclonal antibodies and JAK inhibitors have emerged as important agents in the management of COVID-19. Prior to COVID-19, these drugs have primarily been used in treatment of rheumatological conditions, particularly rheumatoid arthritis (RA). Therefore, while the HBVr experience with these drugs is limited in COVID-19, previous rheumatology literature provides some guidance.

Tocilizumab

By blocking IL-6R, tocilizumab attenuates the cytokine storm of severe COVID-19 which is mediated by IL-6. However, IL-6 has been shown to hinder HBV replication at the transcription level and its inhibition may increase the risk of HBVr in infected individuals [45]. In the only study of HBVr among hospitalized COVID-19 patients undergoing tocilizumab treatment, the outcomes of 44 HBsAg-negative, anti-HBc-positive patients were described [40]. Over half (61%) of these patients received prophylactic entecavir prior to tocilizumab treatment. After a short follow-up of only 1–2 months, no patients experienced HBsAg seroreversion while 1/17 (5.9%) patients not receiving NA prophylaxis developed detectable HBV DNA, but below the quantification limit (< 10 IU/mL) with normal ALT after a single dose of tocilizumab.

More data on HBVr following tocilizumab therapy exist from its established use in RA. Case reports of serious and even fatal HBV flares in HBsAg-positive patients with RA after tocilizumab have been described [46, 47]. As such antivirals are often commenced in these patients prior to treatment, thus limiting their representation in the literature. Only two tocilizumab studies have described HBsAg-positive patients (combined $n = 16$) [40, 48–50]. Of these, 6/10 (60%) developed HBVr in those who did not receive NA prophylaxis (usually due to patient choice) compared to 0/6 in those who did. Of the six HBVr cases, three had virological reactivations with normal ALT while three had biochemical flares (ALT 150–950 U/L) including two patients with jaundice. All received antiviral therapy and recovered from their HBVr. Therefore, there is a high risk (> 10%) of HBVr after tocilizumab in HBsAg-positive patients with ALT elevation and jaundice seen in 50% and 33%, respectively.

Regarding HBsAg-negative, anti-HBc-positive patients, a recent systematic review identified eight observational cohorts (almost all with past HBV infection) receiving tocilizumab [51]. These studies revealed the HBVr rate among HBsAg-negative, anti-HBc-positive patients (albeit using slightly different definitions) ranged from 0 to 11.1% with a pooled rate of 5/192 (2.6%) in those not taking prophylaxis and 0/42 (0%) in those taking NA prophylaxis. Therefore, there appears to be a moderate (1–10%) risk of HBVr following tocilizumab in HBsAg-negative, anti-HBc-positive patients. Compared with HBsAg-positive HBVr, the severity of these

Table 2 Studies on HBV reactivation in patients treated with immunosuppressive therapy

Studies (Location and year)	Indication	Definition of HBVr used	Median/mean follow-up duration	HBV reactivation in HBsAg + patients	HBV reactivation in HBsAg-/anti-HBc + patients
***Dexamethasone* Recommended dose in COVID-19:** 6 mg IV or PO daily for up to 10 days†					
Yip et al. [4] *(Hong Kong, 2021)*	COVID-19	**HBsAg + :** > 1 $\log_{10}$ increase in HBV DNA compared with baseline level	13 days	0/8 (0%) with prophylaxis	Not studied
***Methylprednisolone* Recommended dose in COVID-19:** 32 mg IV or PO daily for up to 10 days†					
Rodriguez-Tajes et al. [40] *(Spain, 2021)*	COVID-19	**HBsAg +** : not defined **HBsAg-/anti-HBc +** : detectable HBV DNA or HBsAg seroreversion‡	1–2 months after last dose	0/3 (0%) with prophylaxis	1/22 (4.5%) without prophylaxis 0/29 (0%) with prophylaxis
Braun-Moscovici et al.[42] *(Israel, 2016)*	Rheumatic diseases (mostly RA)	**HBsAg + or HBsAg-/anti-HBc +** : elevation of ALT three times or more the upper limit of normal and/or > 1 $\log_{10}$ increase of HBV DNA compared with baseline level	4.8 years	0/7 (0%) without prophylaxis and concomitant immunosuppressive therapy 4/9 (44.4%) without prophylaxis and received concomitant DMARDs and/or prednisone 0/2 (0%) with prophylaxis and received concomitant DMARDs and/or prednisone	0/1 (0%) without prophylaxis 1/3 (33.3%) without prophylaxis and received concomitant DMARDs and/or prednisone
***Prednisolone* Recommended dose in COVID-19:** 40 mg IV or PO daily for up to 10 days†					
Wong et al. [43] *(Hong Kong, 2019) ¶*	Not specified	**HBsAg + :** > 1 log10 increase in HBV DNA compared with baseline level	1 year	303/678 (44.7%) without prophylaxis	Not studied
Wong et al. [44] *(Hong Kong, 2020) ¶*	Not specified	**HBsAg-/anti-HBc + :** HBsAg seroreversion	4 years	Not studied	28/502 (5.6%) without prophylaxis
***Hydrocortisone* Recommended dose in COVID-19:** 160 mg IV or PO daily for up to 10 days†					
Yip et al. [4] *(Hong Kong, 2021)*	COVID-19	**HBsAg + :** > 1 $\log_{10}$ increase in HBV DNA compared with baseline level	13 days	0/2 (0%) with prophylaxis	Not studied
***Tocilizumab* Recommended dose in COVID-19:** 8 mg/kg (up to 800 mg) single IV dose					
Rodriguez-Tajes et al.[40] *(Spain, 2021)*	COVID-19	**HBsAg +** : not defined **HBsAg-/anti-HBc +** : detectable HBV DNA or HBsAg seroreversion‡	1–2 months after last dose	0/3 (0%) with prophylaxis	1/17 (5.9%) without prophylaxis 0/27 (0%) with prophylaxis

Table 2 (continued)

Studies (Location and year)	Indication	Definition of HBVr used	Median/mean follow-up duration	HBV reactivation in HBsAg + patients	HBV reactivation in HBsAg-/anti-HBc + patients
Kuo et al. [49] *(Taiwan, 2021)*	RA	**HBsAg +**: > 2 log_{10} increase in HBV DNA compared with baseline level OR HBV DNA > 3 log_{10} IU/mL if previously undetectable HBV DNA OR absolute HBV DNA > 4 log_{10} IU/mL if baseline value unavailable‡ **HBsAg-/anti-HBc +**: detectable HBV DNA OR HBsAg seroreversion‡	9 years	3/3 (100%) without prophylaxis 0/4 (0%) with prophylaxis	1/64 (1.6%) without prophylaxis
Serling-Boyd et al. [60] *(US, 2021)*	RA	**HBsAg-/anti-HBc +**: > 1 log10 increase or absolute increase of 5 log_{10} copies/mL in HBV DNA compared with baseline level OR HBsAg seroreversion	4 years	Not studied	0/12 (0%) without prophylaxis 0/4 (0%) with prophylaxis
Nakamura et al. [71] *(Japan, 2019)*	RA	**HBsAg-/anti-HBc +**: HBV DNA > 2 log_{10} copies/mL	1.5 years	Not studied	2/18 (11.1%) without prophylaxis
Lin et al. [72] *(Taiwan 2019)*	RA	No definition provided	3 years	Not studied	0/11 (0%) without prophylaxis
Watanabe et al. [73] *(Japan 2019)*	RA	**HBsAg-/anti-HBc +**: detectable HBV DNA	1.25 years	Not studied	1/25 (4.0%) without prophylaxis
Ahn et al. [74] *(Korea, 2018)*	RA	**HBsAg-/anti-HBc +**: detectable HBV DNA	10.8 months	Not studied	0/15 (0%) without prophylaxis
Chen et al. [48] *(China, 2017)*	RA	**All:** > 2 log_{10} increase in HBV DNA compared with baseline level OR detectable HBV DNA OR HBsAg or HBeAg seroreversion	3 months	3/5 (60.0%) without prophylaxis 0/2 (0%) with prophylaxis	0/41 (0%) without prophylaxis
Chen et al. [50] *(Taiwan, 2017)*	RA	**HBsAg +:** > 1 log_{10} increase in HBV DNA compared with baseline level OR HBV DNA > 3 × increase in ALT level with HBV DNA > 20,000 IU/mL if baseline value unavailable	28.1 months	0/2 without prophylaxis	Not studied
Mok et al.[75] *(Hong Kong, 2014)*	RA	No definition provided	1.3 years	Not distinguished from past HBV	0/159 (0%) No details given regarding prophylaxis

Table 2 (continued)

Studies (Location and year)	Indication	Definition of HBVr used	Median/mean follow-up duration	HBV reactivation in HBsAg + patients	HBV reactivation in HBsAg-/anti-HBc + patients
Tofacitinib **Recommended dose in COVID-19:** 10 mg PO twice daily for up to 14 days†					
Wang et al.[61] *(Taiwan, 2021)*	RA	**HBsAg +**: > 2 log_{10} increase in HBV DNA compared with baseline level OR HBV DNA > 3 log_{10} IU/mL if previously undetectable HBV DNA OR absolute HBV DNA > 4 log_{10} IU/mL if baseline value unavailable‡ **HBsAg-/anti-HBc +**: detectable HBV DNA OR HBsAg seroreversion‡	Unclear	2/6 (33.3%) without prophylaxis 0/2 (0%) with prophylaxis	2/64 (3.1%) without prophylaxis
Serling-Boyd et al. [60] *(US, 2021)*	RA	**HBsAg-/anti-HBc +**: > 1 log10 increase or absolute increase of 5 log_{10} copies/mL in HBV DNA compared with baseline level OR HBsAg seroreversion	3.1 years	Not studied	0/4 (0%) without prophylaxis 0/2 (0%) with prophylaxis
Chen et al. [59] *(Taiwan, 2018)*	RA	**All:** > 2 log_{10} increase in HBV DNA cases with baseline level	3–6 months after last dose	2/4 (50.0%) without prophylaxis 0/2 (0%) with prophylaxis	0/75 (0%) without prophylaxis
Baricitinib **Recommended dose in COVID-19:** 1–4 mg PO daily depending on eGFR for up to 14 days†					
Rodriguez-Tajes et al. [40] *(Spain, 2021)*	COVID-19	**HBsAg +**: not defined **HBsAg-/anti-HBc +**: detectable HBV DNA or HBsAg seroreversion	1–2 months after last dose	Not studied	0/2 (0%) without prophylaxis
Harigai et al. [62] *(Japan, 2021)*	RA	**HBsAg-/anti-HBc +**: ≥ 2 log increase from baseline levels or new appearance of HBV DNA to a level of ≥ 100 IU/mL§	2.4 years	Not studied	4/215 (1.9%) without prophylaxis But 32/215 (14.9%) if using detectable HBV DNA as definition of HBVr

ALT = alanine aminotransferase, anti-Hbc = antibody to hepatitis B core antigen, HBeAg = hepatitis B e antigen, HBsAg = hepatitis B surface antigen, HBV = hepatitis B virus, HBVr = hepatitis B virus reactivation, RA = rheumatoid arthritis

†Or until hospital discharge

‡American Association for the Study of Liver Diseases guidelines definition [64]

§Asian Pacific clinical practice guidelines definition [12, 65]

¶All steroid uses were standardized to prednisolone equivalent dose reactivations was milder as 4/5 cases had re-emergence of detectable HBV DNA at low levels (< 20 IU/mL), no HBsAg seroreversion, normal ALT levels, and no need for antiviral therapy.

Large pooled studies of HBsAg-negative/anti-HBc-positive patients receiving biologic agents (including tocilizumab) have identified no anti-HBs to be an independent risk factor for HBVr [52–54]. Therefore, anti-HBs titres may be used to further sub-stratify HBVr risk in patients with past HBV infection. However, more data are needed before recommendations can be made for specific agents.

Sarilumab

Sarilumab is an alternative IL-6R for COVID-19 if tocilizumab is not available or feasible to use [19]. There are currently no data on HBVr following sarilumab in either COVID-19 or RA patients. Since both drugs work on the same target, it is reasonable to conclude that the HBVr risk for sarilumab is similar to that of tocilizumab. Indeed, when used at recommended doses for COVID-19 or RA treatment, both drugs have similar IL-6R occupancy and clinical activity [55]. Siltuximab (antibody against IL-6 itself) is another agent blocking the same pathway which has been used to treat COVID-19 [56]. Although HBVr has been reported after siltuximab treatment for COVID-19 [40], the exact risk is not known in COVID or RA patients.

Tofacitinib

Tofacitinib is an oral selective inhibitor of JAK1 and JAK3. It modulates the actions of interferons and IL-6 and suppresses cytokine production, thereby attenuating progressive lung injury from COVID-19 pneumonia [20]. JAK signaling is also involved in the immune response in CHB and its inhibition may impair interferon-mediated suppression of viral replication [57, 58]. There are no data on HBVr following tofacitinib for treatment of COVID-19. However, three RA studies report on HBVr with tofacitinib (Table 2): one small study from the US ($n = 6$) and two larger studies from Taiwan ($n = 81$ and $n = 72$) [59–61]. Both Taiwanese studies (using similar HBVr definitions) reported a high reactivation rate of 33–50% after receiving tofacitinib in HBsAg-positive patients not taking HBV antiviral prophylaxis. Again, no HBsAg-positive patient taking NA prophylaxis developed HBVr. Among HBsAg-negative/anti-HBc-positive patients, two of the three studies detected no cases of HBVr while Wang et al. described HBVr in 3.1% of patients not receiving NA prophylaxis [59–61]. Therefore, like tocilizumab, the HBVr risk from tofacitinib seems to be high (> 10%) in HBsAg-positive patients and moderate (1–10%) for HBsAg-negative, anti-HBc-positive patients.

Baricitinib

In Rodriguez-Tajes et al.'s study specific to COVID-19, no HBVr was seen in the two patients on baricitinib, but both were receiving NA prophylaxis (Table 2) [40]. In post-hoc analysis of a multi-national cohort from phase III clinical trials of baricitinib in 2890 patients with RA, there were 215 HBsAg-negative, anti-HBc-positive patients [62]. Of these, four (1.9%) met the study's definition for HBVr (new appearance of HBV DNA to ≥ 100 IU/mL) with HBV DNAs ranging from 256 to 1547 IU/mL. However, a total of 32/215 (14.9%) patients were HBV DNA positive at some point during follow-up (24/32 below the lower limit of detection of 29 IU/mL). Therefore, the rate of HBVr in HBsAg-negative/anti-HBc-positive patients can as high as 14.9% if the definition of any detectable HBV DNA is used which is the case in most studies. Reassuringly, none of these patients developed ALT elevations and only three required antiviral therapy.

Caution with interpreting and applying HBVr data to COVID-19

Several limitations should be considered when interpreting and applying the above results to the COVID-19 setting. First, aside from Rodriguez-Tajes et al.'s Spanish study, there are no other data specific to COVID-19 patients. Instead, HBVr risk is extrapolated from RA patients receiving the same immunosuppressive drugs. Clearly COVID-19 and RA are two different disease processes and their treatment regimens differ. Although these drugs are typically used in combination with corticosteroids or other immunosuppressive drugs in both conditions, the cumulative exposure is much higher in RA patients. For example, in COVID-19, IL-6R antibodies are recommended as single infusions while the JAK inhibitors are recommended for a duration of 14 days [10]. In RA, these drugs may be continued for prolonged periods while they still maintain disease control. Furthermore, use of these biological or targeted synthetic DMARDs in RA patients usually comes after failing to achieved remission with months of conventional synthetic DMARD therapy which also carry a risk of HBVr. Second, even the RA literature regarding HBVr is limited to mostly small single-center studies. Almost all studies are retrospective in nature which may rely on incomplete data, especially HBV DNA and serology, if regular testing is not protocolised post-DMARD therapy [63]. Third, although pooled data from existing small studies can provide more meaningful information, this is made difficult or less accurate by slightly different definitions of

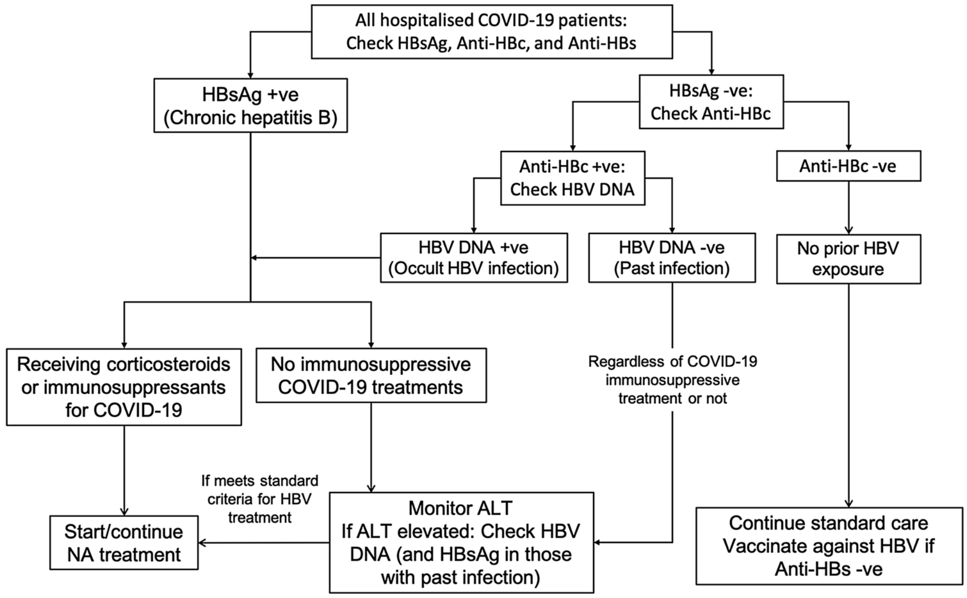

Fig. 1 Algorithm for workup for hepatitis B virus serology and antiviral prophylaxis in patients with chronic hepatitis B who are going to receive COVID-19 immunosuppressive therapies. ALT = alanine aminotransferase; Anti-HBc = antibody to hepatitis B core antigen; anti-HBs = antibody to hepatitis B surface antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; NA = nucleos(t)ide analogue; -ve = negative; + ve = positive

HBVr applied in each study which can over- or underestimate the true HBVr rate. Indeed, only four of the 16 studies listed in Table 2 had adopted a definition provided by international liver societies such as the AASLD or APASL guidelines (which themselves differ in their definition of HBVr) [64, 65]. Importantly, no HBVr has been reported in patients receiving NA prophylaxis, regardless of the definition used. For these reasons, caution needs to be exercised when estimating HBVr risk in COVID-19 following immunosuppressive therapies. Nonetheless, the above data provides clinicians some appreciation of this risk to determine which patients require NA prophylaxis.

Antiviral prophylaxis in CHB patients receiving COVID-19 therapies (Fig. 1)

In HBsAg-positive patients with COVID-19, elevation of serum transaminase levels may be either secondary to HBV or COVID-19 [4]. COVID-19 immunosuppressive therapies (high-dose corticosteroids, tocilizumab/sarilumab, baricitinib and/or tofacitinib) may result in HBV reactivation, hepatitis flare and acute liver failure in patients with current HBV infection [39, 62, 63]. Therefore, antiviral prophylaxis is strongly recommended in all HBsAg-positive patients with severe COVID-19 during corticosteroid and other immunosuppressive therapy [22]. The current recommended first-line NAs with high barrier to resistance (*i.e.* entecavir or tenofovir) should be used for antiviral prophylaxis [12]. The duration of prophylactic NA treatment commenced for patients undergoing immunosuppression is usually 6–12 months after cessation of the immunosuppressive agent(s) [12, 39]. However, virologic and even biochemical relapses commonly occur in CHB patients after stopping NA treatment before HBsAg seroclearance [66, 67]. Therefore, ongoing monitoring of ALT, HBsAg and HBV DNA is recommended after NA withdrawal. In the absence of immunosuppressive therapy, it would also be reasonable to initiate antiviral therapy for HBV whenever the patients fulfill the treatment criteria recommended by international guidelines, namely HBV DNA > 2,000 IU/mL, ALT > upper limit of normal (ULN) (EASL) [68] or 2xULN (AASLD, APASL) [64, 65]. HBsAg-positive patients should also undergo (non-invasive) fibrosis assessment with treatment considered in those with advanced fibrosis or cirrhosis and detectable HBV DNA [12]. If long term therapy is required, the current first-line NAs all have excellent long-term safety [69].

For COVID-19 patients who are HBsAg-negative and anti-HBc-positive, HBV DNA should be checked (for OBI) if corticosteroids and other potent immunosuppressive therapies are anticipated and antiviral therapy with entecavir or tenofovir should be considered if HBV DNA becomes detectable. Monitoring of liver enzymes and repeating HBsAg and HBV DNA at the time of elevation of transaminases would suffice [70].

Conclusion

COVID-19 and current or past HBV infection coexist in a substantial number of people worldwide. With the rapid evolution of COVID-19 treatment, the implications of immunosuppressive regimens on the risk of HBVr must be considered. From the rheumatology experience, there is a high risk of (often serious) HBVr with corticosteroids, IL-6 agents and JAK inhibitors in HBsAg-positive patients. NA prophylaxis is highly effective and recommended in these patients. In past HBV infection, the risk of HBVr is low-moderate and usually not clinically significant. While NA prophylaxis is not generally advised, close monitoring is required. Given the limitations in extrapolating these data, more studies are required to clarify the risk of HBVr with these agents in the context of COVID-19.

Authors' contributions All authors were responsible for the study concept and design. All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors were responsible for the interpretation of data, the drafting, and critical revision of the manuscript for important intellectual content. All authors approved the final version of the article.

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Declarations

Conflict of interest Ken Liu and Madeleine Gill declare no conflict of interest. Terry Yip has served as an advisory committee member and a speaker for Gilead Sciences. Grace Wong has served as an advisory committee member for Gilead Sciences and Janssen, and as a speaker for Abbott, Abbvie, Ascletis, Bristol-Myers Squibb, Echosens, Gilead Sciences, Janssen and Roche. She has also received a research grant from Gilead Sciences.

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