Hepatitis B virus reactivation associated with new classes of immunosuppressants and immunomodulators: A systematic review, meta-analysis, and expert opinion

George V. Papatheodoridis[1,†], Vasileios Lekakis[1,†], Thodoris Voulgaris[1,†], Pietro Lampertico[2,3], Thomas Berg[4], Henry L.Y. Chan[5], Jia-Horng Kao[6], Norah Terrault[7], Anna S. Lok[8,*,#], K. Rajender Reddy[9,*,#]

Summary

HBV reactivation (HBVr) can be prevented by nucleos(t)ide analogues (NAs). We conducted a systematic review and meta-analysis on the risk of HBVr associated with new classes of immunosuppressive and immunomodulatory therapies and developed guidance on NA prophylaxis. An expert panel reviewed the data and categorised the risk of HBVr associated with each class of drugs into low (<1%), intermediate (1-10%), and high (>10%). Our search uncovered 59 studies, including 3,424 HBsAg+ and 5,799 HBsAg-/anti-HBc+ patients, which met our eligibility criteria. Based on medium-high quality evidence, immune checkpoint inhibitors, tyrosine kinase inhibitors, cytokine inhibitors, chimeric antigen receptor T-cell immunotherapies, and corticosteroids were associated with high HBVr risk in HBsAg+ patients; cytokine inhibitors, chimeric antigen receptor T-cell immunotherapies, and corticosteroids with intermediate risk in HBsAg-/anti-HBc+ patients; and anti-tumour necrosis factor agents and immune checkpoint inhibitors with low risk in HBsAg-/anti-HBc+ patients. Provisional recommendations are provided for drugs with low quality evidence. NA prophylaxis is recommended when using drugs associated with a high HBVr risk, while monitoring with on-demand NAs is recommended for low-risk drugs – either approach may be appropriate for intermediate-risk drugs. Consensus on definitions and methods of reporting HBVr, along with inclusion of HBsAg+, and HBsAg-/anti-HBc+ patients in clinical trials, will be key to gathering reliable data on the risk of HBVr associated with immunosuppressive or immunomodulatory therapies.
© 2022 European Association for the Study of the Liver. Published by Elsevier B.V. All rights reserved.

Introduction

HBV reactivation (HBVr) is a serious event which can result in liver failure and death, but it is preventable.[1] HBVr occurs when the immune response of patients with HBV infection is suppressed. It is more common in patients with chronic HBV infection (hepatitis B surface antigen positive [HBsAg+]), but it can also occur in those with past HBV infection regardless of the presence or absence of hepatitis B surface antibody (HBsAg negative, IgG hepatitis B core antibody positive [HBsAg-/anti-HBc+]) because of the persistent presence of HBV DNA in the liver even after serologic recovery.[2,3]

HBVr was first described in patients receiving chemotherapy for malignancies. It has since been reported to be associated with other immunosuppressive therapies including biologics used in a variety of non-malignant diseases, as well as targeted therapies for malignancies. The incidence of HBVr associated with each class of immunosuppressant or immunomodulator is highly varied due to a lack of consensus regarding definitions, and variations in study design and patient selection. Current literature show that B-cell-depleting agents, such as rituximab, are associated with the highest risk of HBVr.[3]

Many comprehensive reviews have been published on the risk of HBVr associated with each class of immunosuppressive therapy, but few have included a meta-analysis of the published studies. Since the publication of the meta-analysis organised by the American Gastroenterological Association in 2015,[4] new classes of immunosuppressants and immunomodulators have been approved for clinical use. Data on the risk of HBVr with these new therapies are sparse. Several professional society guidelines provided recommendations on the prevention of HBVr associated with new classes of immunosuppressants and immunomodulators, but these guidelines focused on select therapies commonly prescribed for diseases within that specialty and most were not accompanied by a systematic review of the published literature.[5–12] We performed a systematic review and meta-analysis on the risk of HBVr associated with new classes of immunosuppressants and immunomodulators used for a broad spectrum of diseases; we also analysed the impact of prophylactic HBV

[1]Academic Department of Gastroenterology, National and Kapodistrian University of Athens, General Hospital of Athens "Laiko", Athens, Greece; [2]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Italy; [3]CRC "A. M. and A. Migliavacca" Center for Liver Disease, Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy; [4]Division of Hepatology, Department of Medicine, Leipzig University Hospital, Leipzig, Germany; [5]Division of Gastroenterology and Hepatology, Union Hospital and Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong; [6]Graduate Institute of Clinical Medicine and Hepatitis Research Center, National Taiwan University College of Medicine and Hospital, Taipei, Taiwan; [7]Division of Gastrointestinal and Liver Diseases, University of Southern California, Los Angeles, California, USA; [8]Division of Gastroenterology and Hepatology, University of Michigan, Ann Arbor, Michigan, USA; [9]Division of Gastroenterology and Hepatology,

antiviral therapy in reducing that risk and provide guidance to physicians across a wide range of specialties. In addition, we reviewed data on 2 commonly prescribed immunosuppressants, corticosteroids and anti-tumour necrosis factor (anti-TNF) agents, to provide updated guidance on risk of HBVr associated with these therapies and indications for prophylactic antiviral therapy.

Methods

Literature search

The literature search was developed in collaboration with an information specialist. All search results were collected using the bibliographic software EndNote. The search was conducted by separately combining HBVr terms with search terms for each drug class in both PubMed and EMBASE. The following search terms were used for HBVr: hepatitis B, hepatitis B virus, hepatitis B surface antigen, hepatitis B antibody, HBV, HBsAg, anti-HBc, anti-HBs, virus activation, virus reactivation, recurrence, recurrent infection, prophylaxis, reactivation, prophylactic, and preempt. The following drug classes were searched: corticosteroids, anti-proliferative agents or antimetabolites, alkylating agents, anti-TNF agents, calcineurin inhibitors, immune checkpoint inhibitors, tyrosine kinase inhibitors, cytokine inhibitors (not including anti-TNF agents), proteasome inhibitors, Janus kinase inhibitors, T cell-depleting agents, adoptive (chimeric antigen receptor [CAR] T-cell) immunotherapy, mammalian target of rapamycin (mTOR) inhibitors, phosphodiesterase inhibitors, integrin inhibitors, chemokine inhibitors, and anti-androgens. The search terms for each drug class included the name of the drug class, the drugs' mechanisms of action and the names of applicable generic drugs within the class. To filter the search results, the drug class search terms were limited, such that only results where the drug class terms could be found in the title, abstract or keywords were collected.

For all drug classes, except for anti-TNF agents, the search was performed from 2010 to 2021. This timeframe was chosen because the focus was on new drugs and new drug classes. For anti-TNF agents, the search extended from 2005 to 2021 to ensure that any search results not captured in the previous review would be included in the present search. After importing all the results into Endnote, de-duplication screening was conducted.

Selection criteria and data extraction

Studies published in English as full papers were included, if they fulfilled all of the following criteria: (1) observational studies (case-control, cross-sectional or cohort) or randomised trials, (2) included patients who were HBsAg+ and/or HBsAg-/anti-HBc+ receiving any of the aforementioned drug classes, except for anti-TNF for which only HBsAg-/anti-HBc+ patients were included,

(3) included patients or subgroups of patients receiving only one drug class and not combinations of >1 drug class, (4) provided data on HBVr based on virological and/or biochemical definitions, and (5) provided data on HBVr separately for each drug class. For drug classes with <5 studies, studies with <5 patients/study were excluded; for drug classes with 5-10 studies, studies with ≤10 patients/study were excluded; and for drug classes with >10 studies, studies with ≤20 patients/study were excluded.

Each study in the list of papers identified by the information specialist was evaluated by 2 independent reviewers (VL, TV) to determine whether it fulfilled all the inclusion criteria. These 2 reviewers extracted data from the selected papers according to a predefined form. The 2 data summary tables were compared for concordance and discrepancies were discussed and arbitrated by a third reviewer (GP). This meta-analysis was conducted based on the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA-P).

Statistical analysis

The outcomes of interest were incidence of HBVr with or without associated hepatitis (biochemical exacerbation), according to the definitions used in each study. For outcomes of HBVr-associated hepatitis, hepatic decompensations, and deaths, events were attributed to HBVr unless otherwise stated. Results were analysed separately for each drug class in patients who did or did not receive prophylactic nucleos(t)ide analogue (NA) therapy, whenever data were available.

Meta-analysis was performed using a generalized linear mixed model.[13] Two-sided confidence intervals for the single proportions of each individual study were calculated using the Clopper and Pearson method.[14] The between-study variance component (τ^2) was estimated applying the maximum likelihood method, based on marginal distribution.[15] Heterogeneity was quantified using I^2 which describes the percentage of total variation across studies that is due to heterogeneity rather than chance.[16] The test statistic was based on a weighted linear regression of the treatment effect on the inverse of the total sample size with weights reciprocal to the variance of the average event probability and followed a t distribution with number of studies -2 degrees of freedom.[17] Pooled proportions or rates and 95% CIs were calculated only if there were ≥3 studies with available data, while the prediction interval defined as the range of true effects expected in future settings was also provided in each figure.[18] A random effects or fixed effect model was applied depending on the existence or not of significant heterogeneity across studies, respectively. Analysis was conducted in R v4.1.2 using meta-packages and metaprop functions.[19]

University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, USA
†Co-first authors.
#Co-senior authors.

* Corresponding authors. Addresses: University of Pennsylvania, 2 Dulles, 3400 Spruce Street, HUP, Philadelphia, PA 19104, United States; Tel.: 215-662-431 (K.R. Reddy), or University of Michigan, 1500 East Medical Center Drive, 3912 Taubman Center, Ann Arbor, MI 48109, United States (A.S. Lok).

E-mail addresses: reddyr@pennmedicine.upenn.edu (K.R. Reddy), aslok@med.umich.edu (A.S. Lok)

Key point

A systematic review and meta-analysis of new classes of immunosuppressants and immunomouldators was performed to assess risk of HBVr.

Results

The initial search produced 1,752 total results. Deduplication screening removed 760 results, producing 992 total unique search results. The drug classes with the highest number of search results included anti-TNF agents, cytokine inhibitors, corticosteroids, and alkylating agents. The searches did not produce any results for integrin inhibitors, chemokine inhibitors and anti-androgens, while there was no study using proteasome or phosphodiesterase inhibitors as the only immunosuppressive agent. Nine-hundred and thirty four studies were excluded: 925 for not fulfilling the inclusion criteria and 9 because the sample sizes were too small, while 1 study was identified through manual search. Thus, 59 studies with a total of 9,223 (3,424 HBsAg+ and 5,799 HBsAg-/anti-HBc+) patients were finally included in this systematic review with 1 study[20] having subgroups of patients receiving 4 and another study[21] having subgroups of patients receiving 2 different classes of agents (Fig. S1). The definitions of virological reactivation or HBVr were variable for HBsAg+ patients, from serum HBV DNA increase by >1-2 $\log_{10}$ IU/ml from baseline to HBV DNA levels >10$^{3-5}$ IU/ml, while they were usually based on detection of HBV DNA and/or HBsAg seroreversion for HBsAg-/anti-HBc+ patients. The definitions of HBVr-associated hepatitis also varied, with most studies using an alanine aminotransferase (ALT) cut-off of >upper limit of normal (ULN) or >3-fold ULN or >100 U/L. Details of the studies, patient characteristics, incidence of HBVr with and without prophylactic NA are provided separately for each drug class.

Anti-TNF agents

There were 18 studies including 1,640 HBsAg-/anti-HBc+ patients receiving anti-TNF agents, 76 of whom received NA prophylaxis (Table 1).[20–37] The pooled HBVr rate was 1% (95% CI 1-2%; heterogeneity, p = 0.35/0.28) overall as well as in the 1,564 patients not receiving NA prophylaxis (Fig. 1A). HBVr was not observed in any of 76 patients receiving NA prophylaxis in 6 studies.[22,26,27,29,35,36] Only 1/1,481 (0.07%) patient not receiving NA prophylaxis developed HBVr-associated hepatitis (pooled rate: 0%, 95% CI 0-0.5%; heterogeneity, p = 1.00) and no patient developed hepatic decompensation or died (Table 2).

Immune checkpoint inhibitors

There were 8 studies with 2,183 patients receiving immune checkpoint inhibitors (Table 3).[38–45] All 8 studies included HBsAg+ patients; HBVr was observed in 18/1,057 (1.7%) patients. The pooled HBVr rate was 3% overall (95% CI 1-9%; heterogeneity, p <0.01), 2% (95% CI 0-7%; heterogeneity, p <0.01) in 1,001 patients receiving (Fig. 2A) and 11% (95% CI 5-22%; heterogeneity, p = 0.34) in 56 patients not receiving NA prophylaxis (Fig. 2B) (Table 4). In 6 studies providing such data,[39–43,45] HBVr-associated hepatitis was observed in 7/644 (1.1%) patients (pooled rate: 1%, 95% CI 1-2%; heterogeneity, p = 0.66) without substantial differences between patients receiving or not receiving NA prophylaxis (4/590 or 0.7% vs. 3/54 or 0.6%). None of 660 HBsAg+ patients experienced liver decompensation or died (Table 4). HBsAg clearance was observed in 3 (0.3%) patients all of whom received NA prophylaxis.

In 7 studies including HBsAg-/anti-HBc+ patients,[38,39,41–45] HBVr developed in only 2/1,126 (0.2%) patients overall (pooled rate: 0%, 95% CI 0-1%; heterogeneity, p = 0.18): 0/120 (0%) in those receiving and 2/1,006 (0.2%) in those not receiving NA prophylaxis (Fig. 1B). HBVr-associated hepatitis, liver decompensation or death was not observed in >600 patients in whom these outcomes were reported (Table 4).

Tyrosine kinase inhibitors

Four studies including 268 patients treated with tyrosine kinase inhibitors were identified (Table 5).[46–49] In 3 studies with 196 HBsAg+ patients of whom 189 did not receive NA prophylaxis,[46,48,49] the pooled rates of HBVr and HBVr-associated hepatitis were 11% (95% CI 7-16%; heterogeneity, p = 0.10/0.08) (Fig. 2C) and 8% (95% CI 5-13%; heterogeneity, p = 0.49), respectively. Only 7 patients received NA prophylaxis,[48] of whom 1 experienced HBVr and none had HBVr-associated hepatitis (Table 6).

In 3 studies with 72 HBsAg-/anti-HBc+ patients[46–48] (Table 5), none of whom received NA prophylaxis, no HBVr was reported (Table 6).

No patient treated with tyrosine kinase inhibitors developed HBVr-related hepatic decompensation or died (Table 6).

Cytokine inhibitors

There were 9 studies including 339 patients receiving only cytokine inhibitors (Table 5).[21,50–57] In 6 studies with 71 HBsAg+ patients,[51–55,57] the pooled HBVr rate was 23% overall (95% CI 14-34%; heterogeneity, p = 0.78): 0/26 patients receiving and 16/45 (35.5%) not receiving NA prophylaxis (pooled rate: 36%, 95% CI 23-50%; heterogeneity, p = 0.73) (Fig. 2D). In the same 6 studies, HBVr-associated hepatitis was observed in 3/71 patients overall (pooled rate: 4%, 95% CI 1-12%; heterogeneity, p = 1.00), and in 3/45 in the subgroup not receiving NA prophylaxis (pooled rate: 7%, 95% CI 2-19%; heterogeneity, p = 1.00) (Table 6).

In 8 studies including 268 HBsAg-/anti-HBc+ patients,[21,50–54,56,57] the pooled HBVr rate was 2% overall (95% CI 1-5%; heterogeneity, p = 1.00): 0/33 patients receiving NA prophylaxis in 1 study[56] and 6/235 patients not receiving NA prophylaxis in 8 studies (pooled rate: 3%, 95% CI 1-6%; heteroge-

Table 1. Main characteristics of studies providing data on HBVr in HBsAg-, anti-HBc+ patients receiving treatment with anti-tumour necrosis factor agents.

| Study | Study design | Me(di)an age, years | Patients, n | HBsAg-, anti-HBc+ patients, n | | | Prophylactic NAs, n | Follow-up, months | Definition of HBVr | Definition of HBVr-associated hepatitis |
				Total	Anti-HBs-	Anti-HBs+				
Caporali 2010[24]	R	57	67	67	39	28	0	43	HBV DNA detectable and/or HBsAg positive	n.a.
Cassano 2011[25]	R	54	62	62	12	50	0	48	HBV DNA detectable and/or HBsAg positive	n.a.
Mori 2011[30]	R	n.a.	31	31	n.a.	n.a.	0	n.a.	HBV DNA detectable	ALT >2xULN
Tamori 2011[36]	R	n.a.	42	42	8	34	1	24	HBV DNA ≥1 log increase or >2.1 log cp/ml	ALT ≥10xULN
Papa 2013[32]	R	54	22	22	n.a.	n.a.	0	n.a.	n.a.	n.a.
Ballanti 2014[22]	R	63	25	25	1	24	2	27	HBsAg positive	n.a.
Ye 2014[37]	R	46	50	50	10	40	0	12	HBV DNA-detectable or >1 log increase	n.a.
Barone 2015[23]	R	n.a.	146	146	0	146	0	56	n.a.	n.a.
Nakamura 2016[31]	R	n.a.	48	48	n.a.	n.a.	0	18	HBV DNA >2 log cp/ml	n.a.
Giannitti 2017[28]	R	61	131	131	n.a.	n.a.	0	75	HBV DNA detectable and/or HBsAg positive	n.a.
Clarke 2018[26]	R	56	120	120	32	88	37	15	HBV DNA detectable	n.a.
Papalopoulos 2018[33]	R	n.a.	111	111	29	82	0	24	HBV DNA ≥1 log increase or reappearance	ALT >2-3xULN
Pauly 2018[34]	R	54	178	178	69	109	0	36	HBV DNA detectable or >2000 IU/ml and/or HBsAg positive	n.a.
Solay 2018[35]	R	n.a.	22	22	n.a.	n.a.	3	n.a.	HBV DNA detectable and/or HBsAg positive	ALT >5xULN
Watanabe 2019[21]	R	n.a.	98	98	10	86	0	15	HBV DNA detectable	n.a.
Tokmak 2021[20]	R	n.a.	111	111	66	45	0	24	HBV DNA-detectable and/or HBsAg positive	n.a.
Fidan 2021[27]	R	52	272	272	31	241	31	33	HBV DNA detectable or ≥1 log increase and/ or HBsAg positive	n.a.
Lee 2021[29]	R	n.a.	104	104	17	87	2	n.a.	HBV DNA detectable or ≥2 log increase	ALT >2xULN

Anti-HBC+, anti-hepatitis B core antibody positive; anti-HBs+/-, anti-hepatitis B surface antibody positive/negative; HBVr, HBV reactivation; NA, nucleos(t)ide analogue; n.a., not available; P, prospective; R, retrospective; ULN, upper limit of normal.

neity, *p* = 0.87) (Fig. 1C).[21,50–54,56,57] In the latter subgroup, HBVr-associated hepatitis occurred in only 1/235 patients (pooled rate: 0%, 95% CI 0-3%; heterogeneity, *p* = 1.00) (Table 6).

No HBVr-related liver decompensation or death was observed among HBsAg+ or HBsAg-/anti-HBc+ patients treated with cytokine inhibitors (Table 6).

T cell-depleting agents
Four studies including 97 HBsAg+ patients treated with T cell-depleting agents were included (Table 7).[20,58–60] In 2 studies,[58,59] HBVr was observed in 4/59 (6.8%) patients, 0/17 receiving and 4/42 (9.5%) not receiving NA prophylaxis (Table 8). In 1 study,[59] 0/51 patients, of whom13 received and 38 did not receive NA prophylaxis, developed HBVr-associated hepatitis.

In 3 studies including 38 HBsAg-/anti-HBc+ patients, of whom 4 received and 34 did not

receive NA prophylaxis,[20,59,60] no HBVr was detected (Table 8).

CAR T-cell immunotherapy
There were 6 studies in patients receiving only CAR T-cell immunotherapy (Table 7).[61–66] In 5 studies,[61,62,64–66] HBVr was observed in 6/57 HBsAg+ patients who received NA prophylaxis (pooled rate: 11%, 95% CI 5-22%; heterogeneity, *p* = 0.81) (Fig. 2E). One of these 57 (1.8%) patients experienced HBVr-associated hepatitis, and none developed hepatic decompensation or died (Table 8).

In 5 studies,[61–65] HBVr was observed in 4/122 (3.3%) HBsAg-/anti-HBc+ patients (pooled rate: 3%, 95% CI 1-8%; heterogeneity, *p* = 0.99): 0/10 receiving and 4/112 (3.6%) not receiving NA prophylaxis (Fig. 1D). Two of the 112 patients not receiving NA prophylaxis experienced HBVr-associated hepatitis (pooled rate: 2%, 95% CI 1-6%;
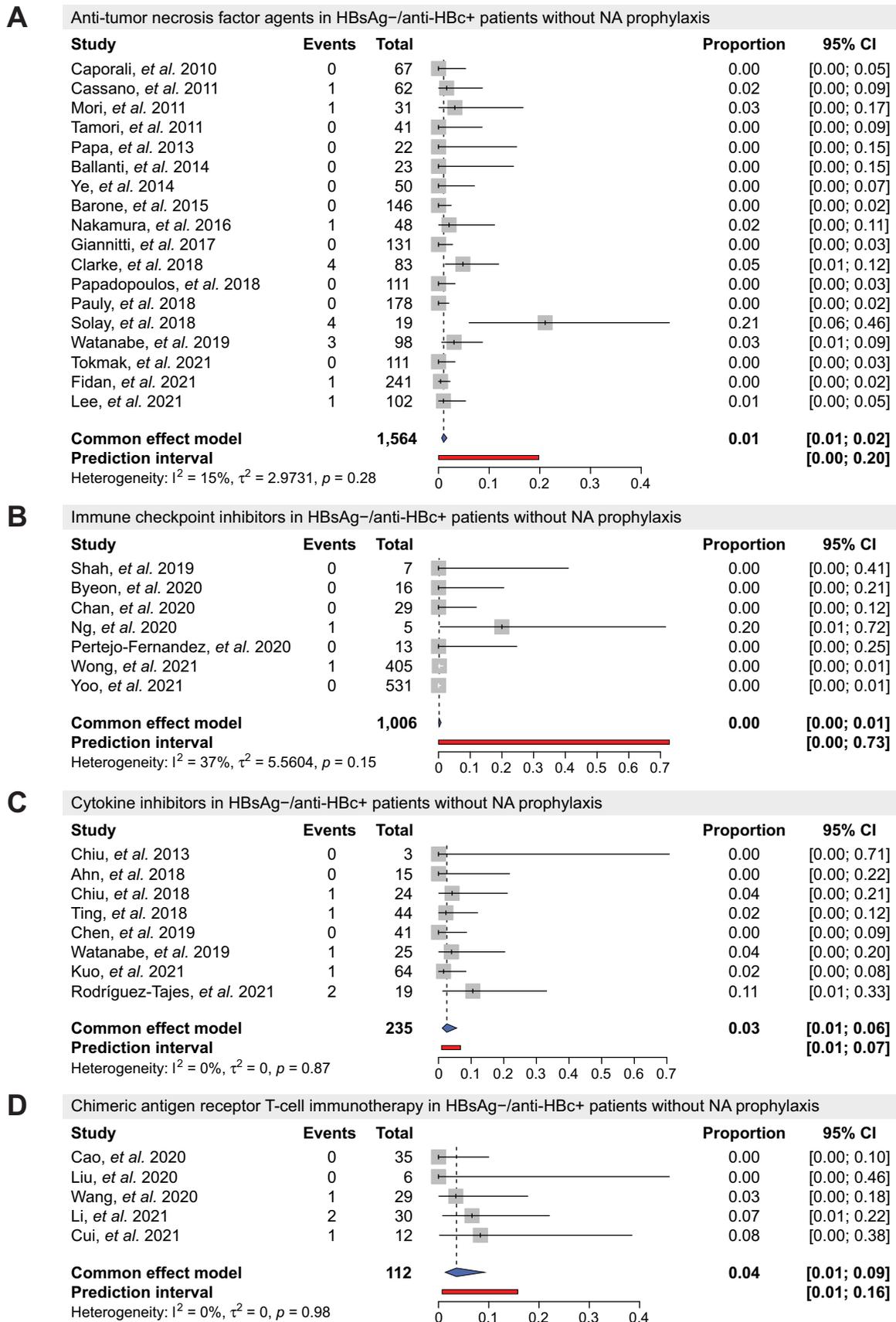
Fig. 1. Pooled rates of HBV reactivation in HBsAg-/anti-HBc+ patients receiving treatments in the absence of NA prophylaxis. (A) Treatment with anti-tumour necrosis factor agents, (B) immune checkpoint inhibitors, (C) cytokine inhibitors or (D) CAR T-cell immunotherapy. CAR, chimeric antigen receptor; NA, nucleos(t)ide analogue.

Table 2. HBVr in HBsAg-, anti-HBc+ patients receiving treatment with anti-tumour necrosis factor agents.

Study	Patients with HBVr, n/N	HBVr in relation to prophylactic NA, n/N		Patients with HBVr-associated hepatitis, n/N	HBVr-associated hepatitis in relation to prophylactic NA, n/N		Liver decompensation, n/N	Death, n/N
		NA	No NA		NA	No NA		
Caporali 2010[24]	0/67	-	0/67	0/67	-	0/67	0/67	0/67
Cassano 2011[25]	1/62	-	1/62	0/62	-	0/62	0/62	0/62
Mori 2011[30]	1/31	-	1/31	0/31	-	0/31	0/31	0/31
Tamori 2011[36]	0/42	0/1	0/41	0/42	0/1	0/41	0/42	0/42
Papa 2013[32]	0/22		0/22	0/22	-	0/22	0/22	0/22
Ballanti 2014[22]	0/25	0/2	0/23	0/25	0/2	0/23	0/25	0/25
Ye 2014[37]	0/50	-	0/50	0/50	-	0/50	0/50	0/50
Barone 2015[23]	0/146	-	0/146	0/146	-	0/146	0/146	0/146
Nakamura 2016[31]	1/48	-	1/48	0/48	-	0/48	0/48	0/48
Giannitti 2017[28]	0/131	-	0/131	0/131	-	0/131	0/131	0/131
Clarke 2018[26]	4/120	0/37	4/83	n.a.	n.a.	n.a.	0/120	0/120
Papalopoulos 2018[33]	0/111	-	0/111	0/111	-	0/111	0/111	0/111
Pauly 2018[34]	0/178	-	0/178	0/178	-	0/178	0/178	0/178
Solay 2018[35]	4/22	0/3	4/19	0/22	0/3	0/19	0/22	0/22
Watanabe 2019[21]	3/98	-	3/98	0/98	-	0/98	0/98	0/98
Tokmak 2021[20]	0/111	-	0/111	0/111	-	0/111	0/111	0/111
Fidan 2021[27]	1/272	0/31	1/241	0/272	0/31	0/241	0/272	0/272
Lee 2021[29]	1/104	0/2	1/102	1/104	0/2	1/102	0/104	0/104

Anti-HBC+, anti-hepatitis B core antibody positive; NA, nucleos(t)ide analogue.

heterogeneity, p = 0.99) and 1 patient developed liver decompensation and died (Table 8).

Corticosteroids

There were 6 studies including 3,866 patients receiving only corticosteroids (Table S1A).[20,67–71] Two studies included 1,728 HBsAg+ patients. In 1 study,[68] 8/72 (11%) patients not receiving NA prophylaxis developed HBVr and all 8 patients were reported to have HBVr-associated hepatitis as well, but none developed liver decompensation or died. In the second study,[71] which only assessed mortality, 36/1,447 (2.5%) patients not receiving but 0/209 receiving NA prophylaxis were reported to have died due to HBVr (Table S2A1). In 4 studies including 2,138 HBsAg-/anti-HBc+ patients, none of whom received NA prophylaxis[20,67,69,70] (Table S1A), the pooled HBVr rate was 3% (95% CI 1-6%; heterogeneity, p <0.01), and no patient died. In 3 of the latter studies providing such data,[20,67,69] only 1/338 (0.3%) patients experienced HBVr-associated hepatitis (pooled rate: 0%, 95% CI 0-2%; heterogeneity, p = 1.00) and no patient developed decompensation (Table S2A2).

Dose and duration of corticosteroids appear to influence the probability of HBVr, but a proper meta-analysis could not be performed due to the heterogeneity of corticosteroid dose groups among studies. In 1 study including 1,800 HBsAg-/anti-HBc+ patients,[70] the probability of HBsAg seroreversion was not associated with corticosteroid dose and duration but the risk of hepatitis flare started to increase in patients receiving corticosteroids at peak daily doses of 20–40 mg or >40 mg prednisolone equivalents given for <7 days (adjusted hazard ratio compared to prednisolone <20 mg for <7 days: 2.19/2.11, p = 0.048/0.015, respectively) and increased further with treatment durations of 7–28 days and >28 days (adjusted hazard ratio 2.02–3.85; p <0.001–0.012). However, the cause of hepatitis flares was not examined in this study and many flares may not be related to HBVr.

Anti-proliferative agents

There were only 2 studies including 87 patients treated with anti-proliferative agents (Table S1B).[20,72] One study[72] included 50 HBsAg+ patients, none of whom received NA prophylaxis; 9 (18%) experienced HBVr, while data on HBVr-associated hepatitis was not provided (Table S2B1). The second study[20] included 37 HBsAg-/anti-HBc+ patients, none of whom received NA prophylaxis; none developed HBVr (Table S2B2).

Alkylating agents

There were only 2 studies including 141 patients treated with alkylating agents (Table S1C).[73,74] One study included 133 HBsAg+ patients,[73] none of whom received NA prophylaxis, HBVr was reported in 17 (12.7%) patients all of whom experienced HBVr-associated hepatitis (Table S2C1). In another study including 8 HBsAg-/anti-HBc+ patients who did not receive NA prophylaxis,[74] no HBVr was observed (Table S2C2).

Calcineurin inhibitors

There were only 2 studies including 145 patients treated exclusively with calcineurin inhibitors (Table S1D).[75,76] In 1 study of HBsAg+ patients, HBVr was reported in 0/4 patients receiving and in 1/4 not receiving NA prophylaxis (Table S2D2).[75] In the second study of 137 HBsAg-/anti-HBc+ patients, none of whom received NA prophylaxis, HBVr was observed in 14 (10.2%), HBVr-associated hepatitis in

Key point

Immune checkpoint inhibitors, tyrosine kinase inhibitors, cytokine inhibitors, CAR T-cell immunotherapies, and corticosteroids were categorized as high risk in HBsAg+ patients.

Table 3. Main characteristics of studies providing data on HBVr in HBsAg+ and/or anti-HBc+ patients receiving treatment with immune checkpoint inhibitors[*].

Study	Study design	Me(di)an age, years	Patients, n	HBsAg+ patients, n	HBsAg-, anti-HBc+ patients, n			Prophylactic NAs, n	Follow-up, months	Definition of HBVr	Definition of HBVr-associated hepatitis
					Total	Anti-HBs-	Anti-HBs+				
Shah 2019[43][*]	R	n.a.	16	8	8	4	4	9	n.a.	n.a.	n.a.
Byeon 2020[38][*]	R	62	32	16	16	n.a.	n.a.	14	3	n.a.	n.a.
Chan 2020[39][*]	R	68	42	8	35	n.a.	n.a.	16	n.a.	HBV DNA ≥2 log increase[1] or ≥3 log[2] or ≥4 log IU/ml[3] or detectable[4] or HBsAg seroreversion[4]	n.a.
Ng 2020[41][#]	R	n.a.	62	55	7	n.a.	n.a.	57	n.a.	HBV DNA ≥1 log increase[1] or detectable[2] or HBsAg seroreversion[4]	ALT ≥3xULN
Lee 2020[40][*]	R-P	61	60	60	0	n.a.	n.a.	54	4-10	HBV DNA ≥1 log increase[1] or ≥3 log IU/ml[2] or HBsAg seroreversion[4]	ALT ≥3xULN & >100 U/L
Pertejo-Fernandez 2020[42]	R	56	16	2	14	n.a.	n.a.	3	20	n.a.	n.a.
Wong 2021[44][#]	R	n.a.	879	397	482	n.a.	n.a.	474	n.a.	HBV DNA ≥2 log increase	n.a.
Yoo 2021[45][#]	R	n.a.	1,075	511	564	n.a.	n.a.	497	n.a.	HBV DNA ≥2 log increase[1] or ≥3 log[2] or ≥4 log IU/ml[3] or detectable[4] or HBsAg seroreversion[4]	ALT >ULN (according to clinicians)

Anti-HBC+, anti-hepatitis B core antibody positive; anti-HBs+/-, anti-hepatitis B surface antibody positive/negative; HBVr, HBV reactivation; NA, nucleos(t)ide analogue; n.a., not available; P, prospective; R, retrospective; ULN, upper limit of normal.

[*]PD-1 inhibitors; ·PD-1 or PD-L1 inhibitors, [#]PD-1 or PD-L1 or CTLA-4 inhibitors.

[1]For patients with detectable HBV DNA at baseline.
[2]For patients with undetectable HBV DNA at baseline.
[3]For patients with unknown HBV DNA levels at baseline.
[4]For patients with negative HBsAg at baseline.

A Immune checkpoint inhibitors in HBsAg+ patients with NA prophylaxis

Study	Events	Total		Proportion	95% CI
Shah, *et al.* 2019	0	8		0.00	[0.00; 0.37]
Byeon, *et al.* 2020	2	14		0.14	[0.02; 0.43]
Chan, *et al.* 2020	1	7		0.14	[0.00; 0.58]
Ng, *et al.* 2020	5	55		0.09	[0.03; 0.20]
Lee, *et al.* 2020	0	54		0.00	[0.00; 0.07]
Pertejo-Fernandez, *et al.* 2020	0	2		0.00	[0.00; 0.84]
Wong, *et al.* 2021	2	397		0.01	[0.00; 0.02]
Yoo, *et al.* 2021	2	464		0.00	[0.00; 0.02]
Random effects model		**1,001**		**0.02**	**[0.00; 0.07]**
Prediction interval					[0.00; 0.51]

Heterogeneity: $I^2 = 74\%$, $\tau^2 = 2.2819$, $p < 0.01$

B Immune checkpoint inhibitors in HBsAg+ patients without NA prophylaxis

Study	Events	Total		Proportion	95% CI
Byeon, *et al.* 2020	1	2		0.50	[0.01; 0.99]
Chan, *et al.* 2020	1	1		1.00	[0.03; 1.00]
Lee, *et al.* 2020	1	6		0.17	[0.00; 0.64]
Yoo, *et al.* 2021	3	47		0.06	[0.01; 0.18]
Common effect model		**56**		**0.11**	**[0.05; 0.22]**
Prediction interval					[0.00; 0.99]

Heterogeneity: $I^2 = 11\%$, $\tau^2 = 0.9213$, $p = 0.34$

C Tyrosine kinase inhibitors in HBsAg+ patients without NA prophylaxis

Study	Events	Total		Proportion	95% CI
Orlandi, *et al.* 2017	0	5		0.00	[0.00; 0.52]
Wang, *et al.* 2019	4	13		0.31	[0.09; 0.61]
Yao, *et al.* 2019	16	171		0.09	[0.05; 0.15]
Random effects model		**189**		**0.11**	**[0.07; 0.16]**
Prediction interval					[0.01; 0.70]

Heterogeneity: $I^2 = 60\%$, $\tau^2 = 0$, $p = 0.08$

D Cytokine inhibitors in HBsAg+ patients without NA prophylaxis

Study	Events	Total		Proportion	95% CI
Chiu, *et al.* 2013	2	7		0.29	[0.04; 0.71]
Chiu, *et al.* 2018	6	22		0.27	[0.11; 0.50]
Ting, *et al.* 2018	2	8		0.25	[0.03; 0.65]
Chen, *et al.* 2019	3	5		0.60	[0.15; 0.95]
Kuo, *et al.* 2021	3	3		1.00	[0.29; 1.00]
Common effect model		**45**		**0.36**	**[0.23; 0.50]**
Prediction interval					[0.17; 0.60]

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.73$

E Chimeric antigen receptor T-cell immunotherapy in HBsAg+ patients with NA prophylaxis

Study	Events	Total		Proportion	95% CI
Cao, *et al.* 2020	1	19		0.05	[0.00; 0.26]
Liu, *et al.* 2020	0	6		0.00	[0.00; 0.46]
Wang, *et al.* 2020	2	12		0.17	[0.02; 0.48]
Yang, *et al.* 2020	3	15		0.20	[0.04; 0.48]
Cui, *et al.* 2021	0	5		0.00	[0.00; 0.52]
Common effect model		**57**		**0.11**	**[0.05; 0.22]**
Prediction interval					[0.03; 0.32]

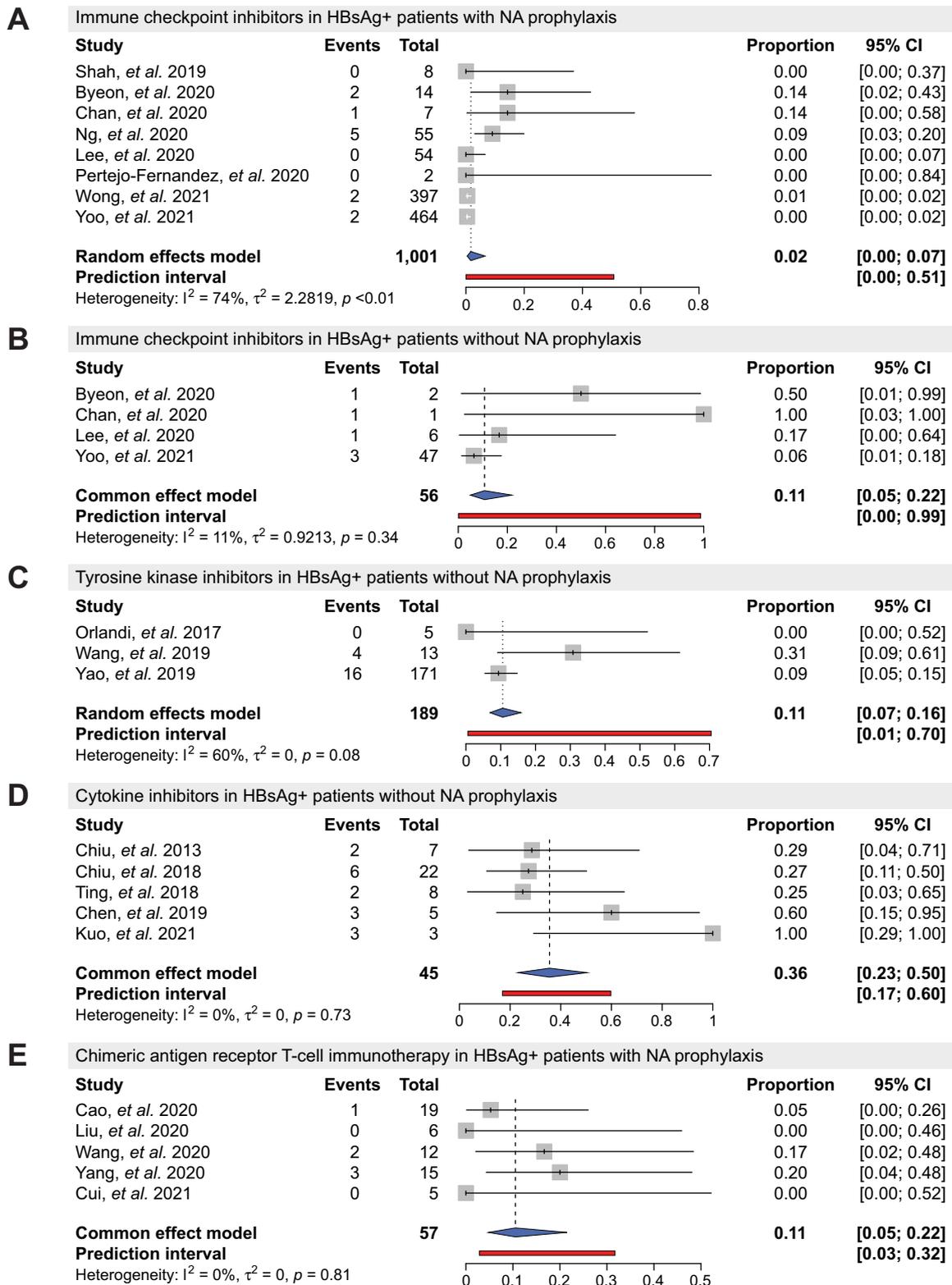Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.81$

Fig. 2. Pooled rates of HBV reactivation in HBsAg+ patients receiving treatment in the absence/presence of NA prophylaxis. (A,B) Treatment with immune checkpoint inhibitors with (A) or without (B) NA prophylaxis; (C) tyrosine kinase inhibitors without NA prophylaxis, (D) cytokine inhibitors without NA prophylaxis, or (E) CAR T-cell immunotherapy with NA prophylaxis. CAR, chimeric antigen receptor; NA, nucleos(t)ide analogue.

6 (4.4%), and liver decompensation and death in 3 (2.2%) patients (Table S2D2).[76]

mTOR inhibitors

There was only 1 study on mTOR inhibitors, which included 27 HBsAg+ patients (Table S1E).[77] HBVr-associated hepatitis was observed in 4/26 patients who did not receive NA prophylaxis; HBV DNA testing showed that all 4 patients had HBVr. None developed decompensation or died (Table S1F).

Janus kinase inhibitors

There was no study on Janus kinase inhibitor monotherapy in HBsAg+ patients and only 1 study in HBsAg-/anti-HBc+ patients. None of the 213 patients in this study received NA prophylaxis (Table S1F).[78] HBVr was observed in 30 (14.1%) patients, but none developed HBVr-associated hepatitis or liver decompensation (Table S2F).

Discussion

HBVr can be associated with a wide spectrum of immunosuppressants and immunomodulators. Because HBsAg+ and often HBsAg-/anti-HBc+ patients are excluded from clinical trials of immunosuppressants and immunomodulators, the incidence of HBVr associated with these therapies is unknown. Yet, when new immunosuppressants and immunomodulators are approved, they are used in patients with chronic or past HBV infection. While universal use of NA prophylaxis might prevent most if not all cases of HBVr, its use may not be necessary if the risk of HBVr is low. We conducted a systematic review of available publications up to 2021, and when possible meta-analyses to provide an estimate of the risk of HBVr associated with new classes of immunosuppressants and immunomodulators to guide the use of NA prophylaxis.

In the 2015 systematic review organised by the American Gastroenterological Association,[4,11] the risk of HBVr associated with anti-TNF agents in HBsAg-/anti-HBc+ patients was rated as moderate. Our updated meta-analysis including 18 studies and 1,564 HBsAg-/anti-HBc+ patients receiving anti-TNF agents and no NA prophylaxis yielded a pooled HBVr risk of 1% (95% CI 1-2%) (Fig. 1A). While the pooled risk of 1% would marginally categorise the risk of HBVr as intermediate, HBVr-associated hepatitis developed in <0.1% (1/1481) of such patients without NA prophylaxis and no patient developed hepatic decompensation or died. In addition, data from recent large (>100 patients) studies indicate that the risk of HBVr associated with anti-TNF agents in HBsAg-/anti-HBc+ patients should be categorised as low. Specifically, 5 studies with a total of 677 patients (111-178 in each study) reported no HBVr,[20,23,28,33,34] and 2 studies with 102 and 241 patients reported HBVr in 1 patient each.[27,29] We did not evaluate the risk of HBVr associated with anti-TNF agents in HBsAg+

patients, which was rated as moderate in the 2015 systematic review,[4,11] though recent studies showed that risk is high and most experts agree that NA prophylaxis is indicated.[8,9]

Immune checkpoint inhibitors have revolutionised the treatment of a wide variety of malignancies. While their primary action is to remove immune blockade hence enabling the immune destruction of tumour cells, it is unclear if immune checkpoint inhibitors can cause HBVr. A review of 8 studies including 1,001 HBsAg+ patients receiving NA prophylaxis[38–40,42–45,61] showed that the pooled rate of HBVr was 2% (95% CI 0-7%) overall but only 0.5% (4/861) when data were limited to 2 large studies.[44,45] The risk of HBVr among HBsAg+ patients not receiving NA prophylaxis was higher, with a pooled rate of 11% (95% CI 5-22%) but there were only 4 studies[38–40,45] with a total of 56 patients and the risk was 6% (3/47) in the largest study.[45] While the studies analysed indicated that the patients received immune checkpoint inhibitors only, given the frequent occurrence of immune-mediated adverse events necessitating high dose corticosteroids, it is unclear if all cases of HBVr can be solely attributed to immune checkpoint inhibitors. Moreover, most patients in these studies had advanced stage solid cancers and possible immune impairment from previous therapies or advanced malignancies, and many had hepatocellular carcinoma. Nonetheless, until further data are available, NA prophylaxis should be recommended in HBsAg+ patients who will be receiving immune checkpoint inhibitors. By contrast, only 2/1,006 (0.2%) HBsAg-/anti-HBc+ patients receiving immune checkpoint inhibitors and no NA prophylaxis were observed to have HBVr (Fig. 1B) suggesting that monitoring and on-demand NA therapy suffice for these patients.

Many kinase inhibitors have been approved for treatment of malignancies in the last 30 years, with many more in clinical trials. We found only 4 studies[46–49] of patients receiving tyrosine kinase inhibitors alone, with pooled rates of HBVr of 11% (95% CI 7-16%) in 189 HBsAg+ patients not receiving NA prophylaxis (Fig. 2C), while no cases of HBVr were reported in 72 HBsAg-/anti-HBc+ patients not receiving NA prophylaxis, suggesting a need for NA prophylaxis in HBsAg+ but not in HBsAg-/anti-HBc+ patients.

Several cytokine inhibitors have been approved for treatment of rheumatologic, gastrointestinal, and dermatologic conditions in recent years. We found 9 studies reporting on HBVr in patients receiving cytokine inhibitors alone,[21,50–57] but the number of patients in each study was small (range 3-64). Thus, while the pooled rate of HBVr of 36% (95% CI 23-50%) in HBsAg+ patients not receiving NA prophylaxis (Fig. 2D) suggest an indication for NA prophylaxis in HBsAg+ patients, more data are needed. By contrast, the pooled rate of HBVr was lower: 3% (95% CI 1-6%) in 235 HBsAg-/anti-HBc+

Table 4. HBVr in HBsAg+ and/or anti-HBc+ patients receiving treatment with immune checkpoint inhibitors.

Study	Patients with HBVr, n/N	HBVr in relation to prophylactic NA, n/N		Patients with HBVr-associated hepatitis, n/N	HBVr-associated hepatitis in relation to prophylactic NA, n/N		Liver decompensation, n/N	Death, n/N
		NA	No NA		NA	No NA		
HBsAg+ patients								
Shah 2019[43]	0/8	0/8	-	0/8	0/8	-	0/8	0/8
Byeon 2020[38]	3/16	2/14	1/2	n.a.	n.a.	n.a.	0/16	0/16
Chan 2020[39]	2/8	1/7	1/1	0/8	0/7	0/1	0/8	0/8
Ng 2020[41]	5/55	5/55	-	2/55	2/55		0/55	0/55
Lee 2020[40]	1/60	0/54	1/6	1/60	0/54	1/6	0/60	0/60
Pertejo-Fernandez 2020[42]	0/2	0/2	-	0/2	0/2	-	0/2	0/2
Wong 2021[44]	2/397	2/397	-	n.a.	n.a.	-	n.a.	n.a.
Yoo 2021[45]	5/511	2/464	3/47	4/511	2/464	2/47	0/511	0/511
HBsAg-, anti-HBc+ patients								
Byeon 2020[38]	0/16	-	0/16	n.a.	n.a.	n.a.	0/16	0/16
Shah 2019[43]	0/8	0/1	0/7	0/8	0/1	0/7	0/8	0/8
Chan 2020[39]	0/35	0/6	0/29	0/35	0/6	0/29	0/35	0/35
Ng 2020[41]	1/7	0/2	1/5	n.a.	n.a.	n.a.	0/7	0/7
Pertejo-Fernandez 2020[42]	0/14	0/1	0/13	0/14	0/1	0/13	0/14	0/14
Wong 2021[44]	1/482	0/77	1/405	n.a.	n.a.	n.a.	n.a.	n.a.
Yoo 2021[45]	0/564	0/33	0/531	0/564	0/33	0/564	0/564	0/564

Anti-HBC+, anti-hepatitis B core antibody positive; HBVr, HBV reactivation; NA, nucleos(t)ide analogue, n.a., not available.

patients not receiving NA prophylaxis with 1 study of 19 patients accounting for 40% of HBVr cases,[56] suggesting NA prophylaxis may not be necessary (Fig. 1C).

Janus kinase inhibitors are used in the treatment of many immune-mediated and inflammatory diseases including rheumatoid arthritis, inflammatory bowel disease, atopic dermatitis as well as hematologic disorders such as myelofibrosis and graft-versus-host disease. We found only 1 study with HBVr in 30/213 (14%) HBsAg-/anti-HBc+ patients not receiving NA prophylaxis,[78] but none experienced HBVr-associated hepatitis, hepatic decompensation, or death.

T cell-depleting agents are used in rheumatologic conditions. Only 4 studies reporting on HBVr were found.[20,58–60] HBVr was observed in only 1 study where all 4 HBsAg+ patients not receiving NA prophylaxis had HBVr,[58] but HBVr was not observed in 38 HBsAg+ patients in another study[59] or in 34 HBsAg-/anti-HBc+ patients not receiving NA prophylaxis in 3 studies.[20,59,60] While these data are limited, they suggest the risk of HBVr associated with T cell-depleting agents is lower than for B cell-depleting agents where the risk of HBVr is approximately 40% in HBsAg+ and 10% in HBsAg-/anti-HBc+ patients not receiving NA prophylaxis, though the risk appears to be lower when B cell-depleting agents are used as monotherapy.[79–81] Traditionally, T cells are thought to be more important for immune control of chronic HBV infection than B cells.[6,12] These data on risk of HBVr associated with T cell-depleting agents, if confirmed, should prompt re-examination of the role of B cells in chronic HBV infection.

CAR T-cell immunotherapy is increasingly used in the treatment of hematologic malignancies; we found 6 relevant studies on HBVr.[61–66] Among 57 HBsAg+ patients (all under NA prophylaxis) included in 5 studies, the pooled HBVr rate was 11% (95% CI 5-22%) (Fig. 2E),[61,62,64–66] but only 1 patient developed HBVr-associated hepatitis.[65] The high rate of HBVr in patients receiving NA prophylaxis is surprising and may be related to factors that we were unable to glean from our review, as the HBVr rates in these 5 studies varied widely from 0% in 2 studies to 20% in 1 study. Among HBsAg-/anti-HBc+ patients, none of 10 patients receiving NA prophylaxis developed HBVr, while the pooled HBVr rate among 112 patients not receiving NA prophylaxis was 4% (95% CI 1-9%) (Fig. 1D).[61–65] While data are limited, they suggest NA prophylaxis is indicated and should be given for longer, like for B cell-depleting therapy, as immune suppression with CAR T-cell therapy may last for long durations.

In addition to new classes of immunosuppressants and immunomodulators, we also reviewed the literature on several classes of widely used immunosuppressants to determine if new data can provide a more accurate estimate of the risk of HBVr. The risk of HBVr associated with corticosteroids is well known, but it remains unclear at what dose/duration the risk is high enough to warrant NA prophylaxis in HBsAg+ and in HBsAg-/anti-HBc+ patients. Our search yielded only 1 study[70] that addressed this question. That study examined hepatitis flares but did not determine whether those flares were related to HBVr.

There have been concerns of HBVr in patients with COVID-19 where such patients are treated with dexamethasone, tocilizumab (anti-IL6 receptor antagonist) or baricitinib (Janus kinase inhibitor). In an observational study of 72 patients with evidence of past or ongoing HBV infection (69 HBsAg-/anti-HBc+, of whom 38 were on NA prophylaxis, and 3 HBsAg+) who received a variety of

Key point

Cytokine inhibitors, CAR T-cell immunotherapies, and corticosteroids were categorized as intermediate risk in HBsAg-/anti-HBc+ patients.

Table 5. Main characteristics of studies providing data on HBVr in HBsAg+ and/or anti-HBc+ patients receiving treatment with tyrosine kinase or cytokine inhibitors.

Study	Study design	Me(di)an age, years	Patients, n	HBsAg+ patients, n	HBsAg-, anti-HBc+ patients, n			Prophylactic NAs, n	Follow-up, months	Definition of HBVr	Definition of HBVr-associated hepatitis
					Total	Anti-HBs-	Anti-HBs+				
Tyrosine kinase inhibitors											
Orlandi 2017[46]*	R	53	32	6	26	n.a.	n.a.	1	112	HBV DNA >2 log increase or reappearance	n.a.
Sora 2017[47]˄	R	65	10	0	10	1	9	0	46	HBV DNA reappearance & ALT >ULN	ALT >3xULN or >100 U/L
Wang 2019[48]#	R	48	55	19	36	n.a.	n.a.	6	44	HBV DNA >1 log increase or reappearance or >20,000 IU/ml[1]	ALT >100 U/L
Yao 2019[49]!	R	62	171	171	0	-	-	0	26	HBV DNA >1 log increase or >10^5 IU/ml & ALT >ULN	ALT ≥2-fold increase
Cytokine inhibitors											
Chiu 2013[52]*	R	40	14	11	3	1	2	4	10	HBV DNA >1 log increase[1] or >6 log[1] or detectable[2]	n.a.
Ahn 2018[50]˄	R	57	15	0	15	3	12	0	9	HBV DNA detectable	n.a.
Chiu 2018[53]#	P	55	49	25	24	11	13	3	9	HBV DNA >1 log increase[1] or detectable[2] or HBeAg seroreversion	ALT >3-fold increase or >100 U/L
Ting 2018[57]*	P	45	54	10	44	6	38	2	24	HBV DNA >2 log increase[1] or >20,000[1] or >100[2] IU/ml	ALT >2xULN
Chen 2019[51]˄	P	46	48	7	41	9	32	2	20	HBV DNA >1 log increase[1] or detectable[2] or HBsAg/HBeAg seroreversion	n.a.
Lin 2019[55]˄	R	59	11	11	0	-	-	11	36	HBV DNA >1 log increase or >2.6 log cp/ml	ALT >3-fold increase or >100 U/L
Watanabe 2019[21]˄	R	68	25	0	25	4	21	0	15	HBV DNA detectable	n.a.
Kuo 2021[54]˄	R	64	71	7	64	n.a.	n.a.	4	108	HBV DNA >2 log increase[1] or >4 log[1] or >3 log[2] IU/ml	ALT >3-fold increase and >100 U/L
Rodríguez-Tajes 2021[56]˄!	P	67	52	0	52	n.a.	n.a.	33	2	HBV DNA detectable or HBsAg positive	n.a.

Anti-HBC+, anti-hepatitis B core antibody positive; anti-HBs+/-, anti-hepatitis B surface antibody positive/negative; HBVr, HBV reactivation; NA, nucleos(t)ide analogue; n.a., not available; P, prospective; R, retrospective; ULN, upper limit of normal.
Tyrosine inhibitors: *Imatinib, dasatinib, nilotinib or combinations, ˄imatinib or nilotinib, #ponatinib, imatinib, dasatinib, nilotinib or combinations, !osimertinib, gefitinib, afitinib or erlotinib.
Cytokine inhibitors: *Ustekinumab, ˄tocilizumab, #secukinumab, !siltuximab.
[1]In patients with detectable baseline HBV DNA.
[2]In patients with undetectable baseline HBV DNA.

Table 6. HBVr in HBsAg+ and/or anti-HBc+ patients receiving treatment with tyrosine kinase or cytokine inhibitors.

Study	Patients with HBVr, n/N	HBVr in relation to prophylactic NA, n/N		Patients with HBVr-associated hepatitis, n/N	HBVr-associated hepatitis in relation to prophylactic NA, n/N		Liver decompensation, n/N	Death, n/N
		NA	No NA		NA	No NA		
Tyrosine kinase inhibitors – HBsAg+ patients								
Orlandi 2017[46]	0/6	0/1	0/5	0/6	0/1	0/5	0/6	0/6
Wang 2019[48]	5/19	1/6	4/13	3/19	0/6	3/13	n.a.	0/19
Yao 2019[49]	16/171	-	16/171	13/171	-	13/171	n.a.	0/171
Tyrosine kinase inhibitors – HBsAg-, anti-HBc+ patients								
Orlandi 2017[46]	0/26	-	0/26	0/26	-	0/26	0/26	0/26
Sora 2017[47]	0/10	-	0/10	0/10	-	0/10	n.a.	0/10
Wang 2019[48]	0/36	-	0/36	0/36	-	0/36	n.a.	0/36
Cytokine inhibitors – HBsAg+ patients								
Chiu 2013[52]	2/11	0/4	2/7	0/11	0/4	0/7	0/11	0/11
Chiu 2018[53]	6/25	0/3	6/22	0/25	0/3	0/22	0/25	0/25
Ting 2018[57]	2/10	0/2	2/8	0/10	0/2	0/8	0/10	0/10
Chen 2019[51]	3/7	0/2	3/5	0/7	0/2	0/5	n.a.	0/7
Lin 2019[55]	0/11	0/11	-	0/11	0/11	-	0/11	0/11
Kuo 2021[54]	3/7	0/4	3/3	3/7	0/4	3/3	0/7	0/7
Cytokine inhibitors – HBsAg-, anti-HBc+ patients								
Chiu 2013[52]	0/3	-	0/3	0/3	-	0/3	0/3	0/3
Ahn 2018[50]	0/15	-	0/15	0/15	-	0/15	0/15	0/15
Chiu 2018[53]	1/24	-	1/24	0/24	-	0/24	0/24	0/24
Ting 2018[57]	1/44	-	1/44	1/44	-	1/44	0/44	0/44
Chen 2019[51]	0/41	-	0/41	0/41	-	0/41	0/41	0/41
Watanabe 2019[21]	1/25	-	1/25	0/25	-	0/25	0/25	0/25
Kuo 2021[54]	1/64	-	1/64	0/64	-	0/64	0/64	0/64
Rodríguez-Tajes 2021[56]	2/52	0/33	2/19	0/52	0/33	0/19	0/52	0/52

Anti-HBC+, anti-hepatitis B core antibody positive; HBV, HBV reactivation; NA, nucleos(t)ide analogue; n.a., not available.

treatments that included corticosteroids, anti-IL-6 receptor antagonists, and Janus kinase inhibitors for COVID-19, there were no clear cut cases of HBVr.[56] Among the 57 HBsAg-/anti-HBc+ patients with follow-up HBV testing, there were no cases of HBsAg seroreversion. Two had detectable but not quantifiable HBV DNA, both were anti-HBs- at baseline and did not receive NA prophylaxis. All 3 HBsAg+ patients received NAs and none had HBVr. The low rate of HBVr could partly be attributed to NA prophylaxis used in many of the patients and the incomplete follow-up. While the risk of HBVr associated with treatment for COVID-19 is uncertain, it would be reasonable to recommend NA prophylaxis particularly in HBsAg+ patients. Dexamethasone at the doses used for COVID-19 on their own would be associated with a high risk of HBVr in HBsAg+ patients and intermediate risk in HBsAg-/anti-HBc+ patients.

We also searched for updated data on antiproliferative agents, alkylating agents, calcineurin inhibitors and mTOR inhibitors and did not find robust data on the risk of HBVr in HBsAg+ or HBsAg-/anti-HBc+ patients not receiving NA prophylaxis. Risk of HBVr in HBsAg-/anti-HBc+ patients receiving calcineurin inhibitor monotherapy was 10%, but this was based on only 1 study and was rated as intermediate based on low quality evidence and the experience of the expert panel.

Our study focused on HBVr, evidence of increased HBV replication, and not on HBVr-associated hepatitis because mild increases in ALT (1-3x ULN or >100 U/L) are not uncommon in patients with inflammatory disorders or malignancies and may be caused by the underlying disease, concomitant medications, other infections or HBVr. In studies where patient selection was not based on hepatitis flares, 22% (23/105) of patients with HBVr in the absence of NA prophylaxis experienced HBVr-associated hepatitis. Among these studies, hepatic decompensation and death were reported in only 1 patient receiving CAR T-cell immunotherapy. It is possible that the overall favourable outcome associated with HBVr in recent studies is related to increased awareness of HBVr leading to closer monitoring of ALT (with or without HBV markers) in patients receiving immunosuppressants or immunomodulators and prompt initiation of NA therapy upon recognition of HBVr. Two studies, 1 involving corticosteroids[71] and 1 mTOR inhibitors,[77] reported identical rates of HBVr and HBVr-associated hepatitis with one of them reporting the same rates of decompensations and deaths[71] because they selected for patients with those outcomes.

Although we conducted a comprehensive literature search, systematic review and meta-analysis of the selected studies, precise estimates of the risk of HBVr are limited by the lack of consensus regarding the definition of outcomes (HBVr and HBVr-associated hepatitis), the retrospective nature of the studies, the variable and non-consecutive selection of patients studied, and the small number of patients included in many studies.

Table 7. Main characteristics of studies providing data on HBVr in HBsAg+ and/or anti-HBc+ patients receiving T cell-depleting agents or CAR T-cell immunotherapy.

Study	Study design	Me(di)an age, years	Patients, n	HBsAg+ patients, n	HBsAg-, anti-HBc+ patients, n			Prophylactic NAs, n	Follow-up, months	Definition of HBVr	Definition of HBVr-associated hepatitis
					Total	Anti-HBs-	Anti-HBs+				
T cell-depleting agents											
Kim 2012[58]*	R	58	8	8	0	-	-	4	19	HBV DNA ≥1-log increase	ALT ≥3-fold increase
Padovan 2016[59]*	R	63	72	51	21	n.a.	n.a.	17	24	HBV DNA >2,000 IU/ml or HBsAg seroreversion	n.a.
Zappulo 2019[60]ˆ	R	39	6	0	6	0	6	0	7.5	n.a.	n.a.
Tokmak 2021[20]*	P	60	11	0	11	n.a.	n.a.	0	25	HBV DNA reappearance	n.a.
CAR T-cell immunotherapy											
Cao 2020[61]	R	28-35	56	19	37	5	32	21	4	HBV DNA ≥2 log increase[1] or ≥3 log IU/ml[2] or HBsAg seroreversion[3]	ALT >5xULN or bilirubin >3xULN
Liu 2020[64]	R	53	17	6	11	1	10	11	10	HBV DNA >1,000 IU/ml and/or HBsAg seroreversion	n.a.
Wang 2020[65]	P	46	41	12	29	3	26	12	9	HBV DNA >1 log increase[1] or detectable[2] or >2000 IU/ml[4] or HBsAg seroreversion[3]	ALT ≥3xULN or >100 U/L
Yang 2020[66]	R	56	15	15	0	0	0	15	n.a.	HBV DNA >1 log increase[1] or detectable[2]	ALT >100 U/L
Li 2021[63]	P	59	30	0	30	9	21	0	12	HBV DNA ≥100 IU/ml on 2 consecutive measurements	ALT 3×ULN
Cui 2021[62]	P	31	20	5	15	4	11	8	10	HBV DNA ≥2 log increase[1] or ≥3 log IU/ml[2] or HBV DNA ≥4 log IU/ml[4] or HBV DNA detectable[3] or HBsAg seroreversion[3]	ALT ≥3xULN and >100 U/L

Anti-HBC+, anti-hepatitis B core antibody positive; anti-HBs+/-, anti-hepatitis B surface antibody positive/negative; CAR, chimeric antigen receptor; HBVr, HBV reactivation; NA, nucleos(t)ide analogue; n.a., not available; P, prospective; R, retrospective; ULN, upper limit of normal.
T cell-depleting agents: *Abatacept, ˆalemtuzumab.
[1]For patients with detectable HBV DNA at baseline.
[2]For patients with undetectable HBV DNA at baseline.
[3]For patients with negative HBsAg at baseline.
[4]For patients with unknown HBV DNA levels at baseline.

Moreover, while we selected for studies where patients were receiving only 1 class of drugs, we cannot be certain if some patients might have received other classes of immunosuppressants or immunomodulators recently or additional classes of drugs for management of adverse events, such as corticosteroids for immune-mediated events associated with immune checkpoint inhibitors. A few studies found high rates of HBVr even among patients receiving NA prophylaxis, though most of these patients had transient detection of low level HBV DNA without ALT elevation. Unfortunately, we were unable to ascertain adherence to NA or the timing of the start of NAs in relation to the timing of the start of immunosuppressive or immunomodulatory therapies and it is possible that HBVr occurred because of NA non-adherence or delay in the start of NAs, particularly in patients with high baseline HBV DNA. Increases in HBV DNA while on NA prophylaxis may also be due to breakthrough infection secondary to selection of antiviral drug resistance variants. Although entecavir or tenofovir were used in the majority of the recent studies, lamivudine was used in a few studies and not specified in some studies. HBVr can occur after NA prophylaxis is stopped, though we were unable to determine how often this was the case in the studies reviewed. The timing of HBVr in relation to the start of immunosuppressant or immunomodulator therapy suggests that most cases were not related to termination of NA prophylaxis.

Given the limitations in quality of data, we invited a panel of experts to review the results from the systematic review and meta-analysis and to rank the risk of HBVr associated with each class of drugs included in this study in HBsAg+ and in HBsAg-/anti-HBc+ patients, as high (>10%), intermediate (1-10%), low (<1%), and unable to determine. These experts were also asked to indicate their recommendation for HBV screening strategy, which tests to use for screening, and proposed nomenclature and definitions for HBVr and associated outcomes. Responses from the expert panel and society guideline recommendations are summarised in Tables 9 and 10 and Fig. 3.[6–12,82] All recent society guidelines recommend HBV screening of all patients who will be receiving any immunosuppressive, cytotoxic or immunomodulatory therapies regardless of perceived risk of HBV infection or HBVr. Recommendation for universal screening stems from the difficulty in implementing risk assessment of HBV infection in clinical practice and data from 1 study in the United States showing that approximately 90% of patients would require HBV screening to achieve a false negative rate <1%, based on the Centers for Disease Control and Prevention hepatitis risk survey.[83] All societies recommend screening with HBsAg and anti-HBc tests.[6–12,82] Some societies also recommend testing for antibody against HBsAg (anti-HBs), and HBV DNA testing in patients found to be positive for HBsAg or anti-HBc. Though the presence of anti-HBs decreases the risk of HBVr in HBsAg-/anti-HBc+ patients, it does not eliminate the risk of HBVr and data are limited with regard to the anti-HBs titre needed for protection. Furthermore, anti-HBs titres have been shown to fall and become undetectable upon immunosuppression.[84,85] Testing for HBV DNA level and assessment of underlying liver disease prior to start of immunosuppressive or immunomodulatory therapies help inform whether HBsAg+ patients meet hepatitis B treatment indications, as these patients will need to continue NAs even after completion of these therapies. For HBsAg+ patients who do not meet indications for hepatitis B treatment and for HBsAg-/anti-HBc+ patients, NA prophylaxis can be stopped 6 months after completion of immunosuppressive or immunomodulatory therapies (>12 months in the case of B cell-depleting agents and perhaps CAR T-cell immunotherapy). HBV DNA testing can also inform the risk of HBVr in HBsAg-/anti-HBc+ patients, as detection of HBV DNA is associated with increased risk of HBVr[86] and most experts would consider those with detectable HBV DNA to have the same risk as HBsAg+ patients.

Given the paucity of data, the expert panel rated the risk of HBVr associated with some classes of new immunosuppressive or immunomodulatory therapies as unknown. In order to provide interim guidance on the need for NA prophylaxis, provisional risk was assigned for these therapies and quality of evidence indicated as low. All experts agreed that prophylactic NAs should be administered to patients who will be receiving therapies associated with high risk of HBVr, while close monitoring and on-demand NA therapy at the first sign of HBVr is recommended for therapies with low risk of HBVr. The experts agreed that either NA prophylaxis or close monitoring and on-demand NAs can be considered for therapies associated with intermediate risk of HBVr, though most leaned towards NA prophylaxis. Monitoring of ALT (with testing for HBV DNA [for HBsAg+ patients] and HBV DNA or HBsAg [for HBsAg-/anti-HBc+ patients] when ALT is elevated) is more practical and more economical, but therapy might not be as effective if initiated after detecting HBVr-associated hepatitis rather than after detection of virological reactivation. Thus, some experts suggest either NA prophylaxis, especially in countries where the cost of generic NAs are lower than that of HBV DNA testing, or monitoring of HBV DNA or HBsAg (in the case of HBsAg-/anti-HBc+ patients) if feasible. Data guiding the frequency of monitoring are limited with most experts recommending every 1-3 months, though adherence to such frequent monitoring in patients on long-term immunosuppressive therapies can be challenging.

The strengths of our study are that we conducted a comprehensive and systematic review of

> **Key point**
>
> NA prophylaxis is recommended when on drugs associated with high HBVr risk, monitoring and on-demand NAs when on low-risk drugs, and either approach may be appropriate for drugs associated with intermediate risk.

Table 8. HBVr in HBsAg+ and/or anti-HBc+ patients receiving T cell-depleting agents or CAR T-cell immunotherapy.

| Study | Patients with HBVr, n/N | HBVr in relation to prophylactic NA, n/N | | Patients with HBVr-associated hepatitis, n/N | HBVr-associated hepatitis in relation to prophylactic NA, n/N | | Liver decompensation, n/N | Death, n/N |
		NA	No NA		NA	No NA		
T cell-depleting agents – HBsAg+ patients								
4/8	0/4	4/4	n.a.				0/8	
0/51	0/13	0/38	0/51	0/13	0/38	0/51	0/51	
T cell-depleting agents – HBsAg-, anti-HBc+ patients								
Padovan 2016[59]	0/21	0/4	0/17	0/21	0/4	0/17	0/21	0/21
Zappulo 2019[60]	0/6	-	0/6	0/6	-	0/6	0/6	0/6
Tokmak 2021[20]	0/11	-	0/11	0/11	-	0/11	0/11	0/11
CAR T-cell immunotherapy – HBsAg+ patients								
Cao 2020[61]	1/19	1/19	-	1/19	1/19	-	0/19	0/19
Liu 2020[64]	0/6	0/6	-	0/6	0/6	-	0/6	0/6
Wang 2020[65]	2/12	2/12	-	0/12	0/8	0/4	0/12	0/12
Yang 2020[66]	3/15	3/15	-	0/15	0/15	-	0/15	0/15
Cui 2021[62]	0/5	0/5	-	0/5	0/5		0/5	0/5
CAR T-cell immunotherapy – HBsAg-, anti-HBc+ patients								
Cao 2020[61]	0/37	0/2	0/35	0/37	0/2	0/35	0/37	0/37
Liu 2020[64]	0/11	0/5	0/6	0/11	0/5	0/6	0/11	0/11
Wang 2020[65]	1/29	-	1/29	0/29	-	1/29	0/29	0/29
Li 2021[63]	2/30	-	2/30	1/30	-	1/30	0/30	0/30
Cui 2021[62]	1/15	0/3	1/12	1/15	0/3	1/12	1/15	1/15

Anti-HBC+, anti-hepatitis B core antibody positive; CAR, chimeric antigen receptor; HBVr, HBV reactivation; NA, nucleos(t)ide analogue; n.a., not available.

Table 9. Recommendations for HBV screening prior to immunosuppressive or immunomodulatory therapies.

Society, year[Ref]	Whom to screen	HBV screening tests
American Gastroenterological Association, 2015[11]	High risk of HBV infection per CDC guidelines Therapies with moderate-high risk of HBVr	HBsAg and anti-HBc HBV DNA if either positive
European Association for the Study of the Liver, 2017[6]	Any immunosuppressive or chemotherapy	HBsAg, anti-HBc, anti-HBs
American Association for the Study of Liver Diseases, 2018[12]	Any immunosuppressive, cytotoxic or immunomodulatory therapy	HBsAg, anti-HBc
American Society of Clinical Oncology, 2020[7]	Any systemic anti-cancer therapy	HBsAg, anti-HBc, anti-HBs
Asian Pacific Association for the Study of the Liver, 2022[8]	Any immunosuppressive therapy	HBsAg, anti-HBc, anti-HBs
European Society of Clinical Microbiology and Infectious Diseases, 2018[10] *	Anti-TNF, anti-CD20, anti-CD52	HBsAg and ant-HBc
American Academy of Dermatology, 2019[9] *	Anti-TNF, anti-IL12, IL13, IL17	HBsAg, anti-HBc, anti-HBs
American College of Rheumatology, 2021[82] *	Disease-modifying antirheumatic drugs	HBsAg and anti-HBc
Authors of current article	Any immunosuppressive or immunomodulatory therapy	HBsAg and anti-HBc HBV DNA if HBsAg+, optional if HBsAg-/anti-HBc+ Anti-HBs optional

Anti-HBC, anti-hepatitis B core antibody; anti-HBs, anti-hepatitis B surface antibody; HBVr, HBV reactivation.
*Recommendations for specific therapies evaluated.

Table 10. HBVr risk associated with immunosuppressive or immunomodulatory therapies without NA prophylaxis.

| Therapy | HBsAg+ patients | | HBsAg-/anti-HBc+ patients | |
	n/N	Pooled risk (95% CI) or overall percent	n/N	Pooled risk (95% CI) or overall percent
Anti-TNF		n.a.	16/1564	1% (1-2%)
Immune check point inhibitors	6/56	11% (5-22%)[1]	2/1,006	0% (0-1%)
Tyrosine kinase inhibitors	20/189	11% (7-16%)	0/72	0%*
Cytokine inhibitors	16/45	36% (23-50%)	6/235	3% (1-6%)
T cell-depleting agents	4/42	9.5%*	0/34	0%*
CAR T-cell immunotherapy	-	Unknown[2]	4/112	4% (1-9%)
Corticosteroids	8/72	11%*	41/2138	3% (1-6%)
Anti-proliferative agents	9/50	18%*	0/37	0%*
Alkylating agents	17/133	13%*	0/8	0%*
Calcineurin inhibitors	1/4	25%*	14/137	10%*
mTOR inhibitors	4/26	15%*	-	Unknown
Janus kinase inhibitors	-	Unknown	30/213	14%*

Anti-HBC+, anti-hepatitis B core antibody positive; CAR, chimeric antigen receptor; HBVr, HBV reactivation.
Pooled risks (95% CIs) are provided for therapies where there were sufficient studies to conduct meta-analysis; overall percent are presented for other therapies (n: number of patients with HBVr, N: number of patients received therapy). There was no significant heterogeneity in any of the below pooled risks, except for that of corticosteroids in HBsAg-/anti-HBc+ patients.
[1] Pooled HBVr risk was 2% (95% CI 0-7%) in 1,001 HBsAg+ patients receiving NA (heterogeneity, p <0.01).
[2] Pooled HBVr risk was 11% (95% CI 5-22%) in 57 HBsAg+ patients receiving NA (heterogeneity, p = 0.81).
*HBVr data based on low quality evidence.

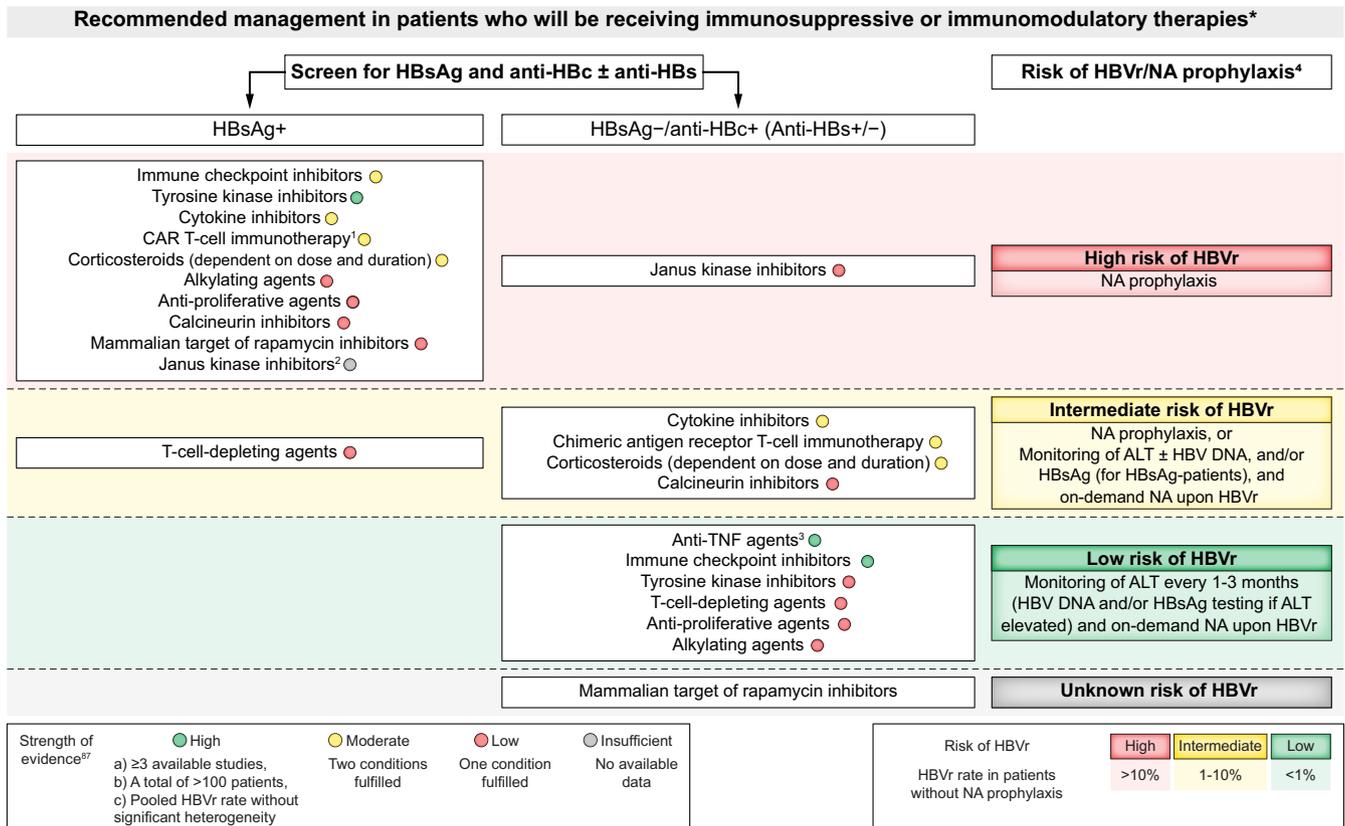**Fig. 3. Recommended management in patients who will be receiving immunosuppressive or immunomodulatory therapies.** [1]Risk estimation based on 11% HBVr risk in HBsAg+ patients receiving CAR T-cell immunotherapy under NA prophylaxis; [2]Risk estimation based on 14% HBVr risk in HBsAg-/anti-HBc+ patients receiving Janus kinase inhibitors without NA prophylaxis; [3]HBVr risk in HBsAg-/anti-HBc+ patients receiving anti-TNF agents was categorised as low based on data from recent large studies and expert opinions, although it was 1% and could be marginally categorised as intermediate; HBVr risk associated with anti-TNF agents in HBsAg+ patients was not assessed (recent studies and most experts agree showed that this risk is high). *Long-term NA therapy is required in HBsAg+ patients who meet hepatitis B treatment indications. Categorization of HBVr risk and recommendations for drug classes with low-quality evidence should be considered provisional. ALT, alanine aminotransferase; anti-HBC+/-, anti-hepatitis B core antibody positive/negative; anti-HBs+/-, anti-hepatitis B surface antibody positive/negative;HBVr, HBV reactivation; NA, nucleos(t)ide analogue.

all published literature up to 2021 on HBVr associated with a wide range of recently approved immunosuppressants and immunomodulators and then estimated the risk of HBVr associated with each class of drugs based on the results of systematic review and meta-analysis, survey of experts, and other society guidelines. Despite our efforts, our estimates of HBVr are imprecise for many classes of drugs. Further, the use as combination regimens in some instances challenges us to identify a specific drug and assign risk for HBVr; thus, we restricted our systematic review and meta-analysis to only studies where a single drug or drug class was used.

In conclusion, the potential for HBVr should be considered during the development of immunosuppressants and immunomodulators. While data on the risk of HBVr might become available as these drugs become more widely used in clinical practice, collaboration between regulatory agencies, the pharmaceutical industry, and experts in disease areas for which new drugs are designed, as well as experts in hepatitis B, is essential to achieve consensus on the definition of HBVr and associated hepatitis flares, and to define selection criteria for studies on HBVr. To expedite and harmonise this process, our expert panel propose nomenclature and definitions for HBVr and associated outcomes based on published guidelines and commonly used definitions among the studies we reviewed (Table 11). The multi-stakeholder collaborative efforts should also address important gaps including optimal frequency of ALT monitoring and the role of HBV DNA and/or HBsAg monitoring in patients receiving drugs associated with intermediate or low risk of HBVr. Given the difficulty in excluding confounders in retrospective studies, future trials of new immunosuppressants and immunomodulators should include HBsAg+ and HBsAg-/anti-HBc+ patients and protocolized monitoring and use of prophylactic or on-demand NA therapy. These trials will generate meaningful

Table 11. Proposed nomenclature and definitions for HBVr and associated outcomes. ̄

	HBsAg+ patients	HBsAg-, anti-HBc+ patients
HBVr#		
	HBV DNA ≥10,000 IU/ml if baseline HBV DNA not available	Seroreversion from HBsAg- to HBsAg+
	HBV DNA ≥1,000 IU/ml if previously undetectable	New detection of quantifiable HBV DNA if previously undetectable
	≥2 $\log_{10}$ increase in HBV DNA if previously detectable	HBV DNA ≥100 IU/ml if previously unknown or detected but not quantifiable
		≥1 $\log_{10}$ increase in HBV DNA if previously quantifiable
HBVr-associated hepatitis*		
If baseline ALT is normal	≥3x ULN	
If baseline ALT is elevated	≥3x baseline	
HBVr-associated severe hepatitis*		
ALT, bilirubin (total), INR	ALT ≥10x ULN or baseline or ALT ≥3x ULN or baseline AND bilirubin >2x ULN or INR >1.5**	
Outcomes of HBVr*		
Liver		
Hepatic decompensation	Ascites, hepatic encephalopathy, variceal bleeding	
Liver-related mortality	Death from liver failure	
Underlying disease		
Treatment interruption	Immunosuppressant or immunomodulator temporarily withheld	
Treatment cessation	Immunosuppressant or immunomodulator stopped with or without switch to alternative therapy	
Mortality from underlying disease	Death due to progression of underlying disease	
All-cause mortality	Death from any cause	

HBV DNA results that are reported as detected but not quantifiable are not always reproducible; thus, quantifiable results are used for defining HBVr.
ALT, alanine aminotransferase; anti-HBC+, anti-hepatitis B core antibody positive; HBVr, HBV reactivation; INR, international normalised ratio; ULN, upper limit of normal.
̄Nomenclature and definitions to be used in clinical trials and in cohort studies.
#Risk of HBVr should be categorised as high (>10%), intermediate (1-10%), or low (<1%).
*Evidence of HBVr present and other causes of outcomes such as sepsis, drug-induced liver injury, hepatic metastasis not present or less likely.
**In the absence of Gilbert's syndrome (for bilirubin) and use of vitamin K antagonists (for INR).

data on the risk of HBVr and the need for NA prophylaxis, both for monotherapies and combinations, which can be used to guide clinical practice following drug approval. As new drugs are approved and new data become available, it is critical that recommendations on preventing HBVr are updated periodically.

Abbreviations
ALT, alanine aminotransferase; anti-HBC+/-, anti-hepatitis B core antibody positive/negative; anti-HBs+/-, anti-hepatitis B surface antibody positive/negative; anti-TNF, anti-tumour necrosis factor; CAR, chimeric antigen receptor; HBVr, HBV reactivation; mTOR, mammalian target of rapamycin; NA, nucleos(t)ide analogue; ULN, upper limit of normal.

the institution) from BMS, Gilead, Merck, Intercept, Sequana, Grifols, BioVie, HCC-TARGET, HCV-TARGET, NASH-TARGET, EXACT Sciences and serves as an advisor to Spark Therapeutics, Mallinckrodt and DSMB-Novartis.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Study concept and design: GP, VL, TV, PL, TB, HC, JHK, NT, AL, KRR. Acquisition of data: GP, VL, TV. Analysis and interpretation of data: GP, VL, TV, AL, KRR. Drafting of the manuscript: GP, AL, KRR. Critical revision of the manuscript for important intellectual content: GP, VL, TV, PL, TB, HC, JHK, NT, AL, KRR. Statistical analysis: GP, VL, TV. Administrative, technical, or material support: GP, AL, KRR. Study supervision: GP, AL, KRR.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2022.07.003.

References

Author names in bold designate shared co-first authorship

[1] Loomba R, Liang TJ. Hepatitis B reactivation associated with immune suppressive and biological modifier therapies: current concepts, management strategies, and future directions. Gastroenterology 2017;152:1297–1309.

[2] Shi Y, Zheng M. Hepatitis B virus persistence and reactivation. BMJ 2020;370:m2200.

[3] Hoofnagle JH. Reactivation of hepatitis B. Hepatology 2009;49:S156–S165.

[4] Perrillo RP, Gish R, Falck-Ytter YT. American Gastroenterological Association Institute technical review on prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. Gastroenterology 2015;148:221–244 e3.

[5] Baddley JW, Cantini F, Goletti D, Gómez-Reino JJ, Mylonakis E, San-Juan R, et al. ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective (Soluble immune effector molecules [I]: anti-tumor necrosis factor-alpha agents). Clin Microbiol Infect 2018;24(Suppl 2):S10–S20.

[6] European Association for the Study of the Liver. Electronic address eee, European Association for the Study of the L. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2017;67:370–398.

[7] Hwang JP, Feld JJ, Hammond SP, Wang SH, Alston-Johnson DE, Cryer DR, et al. Hepatitis B virus screening and management for patients with cancer prior to therapy: ASCO provisional clinical opinion update. J Clin Oncol 2020;38:3698–3715.

[8] Lau G, Yu ML, Wong G, Thompson A, Ghazinian H, Hou JL, et al. APASL clinical practice guideline on hepatitis B reactivation related to the use of immunosuppressive therapy. Hepatol Int 2021;15:1031–1048.

[9] Menter A, Strober BE, Kaplan DH, Kivelevitch D, Farley Prater E, Stoff B. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics. J Am Acad Dermatol 2019;80:1029–1072.

[10] Mikulska M, Lanini S, Gudiol C, Drgona L, Ippolito G, Fernandez-Ruiz M, et al. ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective (Agents targeting lymphoid cells surface antigens [I]: CD19, CD20 and CD52). Clin Microbiol Infect 2018;24(Suppl 2):S71–S82.

[11] Reddy KR, Beavers KL, Hammond SP, Lim JK, Falck-Ytter YT, American Gastroenterological Association. American Gastroenterological Association Institute guideline on the prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. Gastroenterology 2015;148:215–219. ; quiz e16-7.

[12] Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang IP, Jonas MM. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology 2018;67:1560–1599.

[13] Stijnen T, Hamza TH, Ozdemir P. Random effects meta-analysis of event outcome in the framework of the generalized linear mixed model with applications in sparse data. Stat Med 2010;29:3046–3067.

[14] ES CCP. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrica 1934;26:404–413.

[15] Hardy RJ, Thompson SG. A likelihood approach to meta-analysis with random effects. Stat Med 1996;15:619–629.

[16] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–560.

[17] Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Comparison of two methods to detect publication bias in meta-analysis. JAMA 2006;295:676–680.

[18] IntHout J, Ioannidis JP, Rovers MM, Goeman JJ. Plea for routinely presenting prediction intervals in meta-analysis. BMJ Open 2016;6:e010247.

[19] Team RC. R: a language and environment for statistical computing, vol. 2021. Vienna, Austria: R Foundation for Statistical Computing; 2020.

[20] Tokmak S, Gümürdülü Y, Taş DA, Kara IO, Güzel AB. What is the risk of reactivation in patients with Resolved and Past HBV Infection during immunosuppressive therapy if HBV-DNA Negative before treatment? Turkish J Gastroenterol 2021;32:294–301.

[21] Watanabe T, Fukae J, Fukaya S, Sawamukai N, Isobe M, Matsuhashi M, et al. Incidence and risk factors for reactivation from resolved hepatitis B virus in rheumatoid arthritis patients treated with biological disease-modifying antirheumatic drugs. Int J Rheum Dis 2019;22:574–582.

[22] Ballanti E, Conigliaro P, Chimenti MS, Kroegler B, Di Muzio G, Guarino MD, et al. Use of anti-tumor necrosis factor alpha therapy in patients with concurrent rheumatoid arthritis and hepatitis B or hepatitis C: a retrospective analysis of 32 patients. Drug Dev Res 2014;75(Suppl 1):S42–S45.

[23] Barone M, Notarnicola A, Lopalco G, Viggiani MT, Sebastiani F, Covelli M, et al. Safety of long-term biologic therapy in rheumatologic patients with a previously resolved hepatitis B viral infection. Hepatology 2015;62:40–46.

[24] Caporali R, Bobbio-Pallavicini F, Atzeni F, Sakellariou G, Caprioli M, Montecucco C, et al. Safety of tumor necrosis factor alpha blockers in hepatitis B virus occult carriers (hepatitis B surface antigen negative/anti-hepatitis B core antigen positive) with rheumatic diseases. Arthritis Care Res (Hoboken) 2010;62:749–754.

[25] Cassano N, Mastrandrea V, Principi M, Loconsole F, De Tullio N, Di Leo A, et al. Anti-tumor necrosis factor treatment in occult hepatitis B virus infection: a retrospective analysis of 62 patients with psoriatic disease. J Biol Regul Homeost Agents 2011;25:285–289.

[26] Clarke WT, Amin SS, Papamichael K, Feuerstein JD, Cheifetz AS. Patients with core antibody positive and surface antigen negative Hepatitis B (anti-HBc+, HBsAg−) on anti-TNF therapy have a low rate of reactivation. Clin Immunol 2018;191:59–62.

[27] Fidan S, Capkın E, Arıca DA, Durak S, Okatan IE. Risk of hepatitis B reactivation in patients receiving anti-tumor necrosis factor-α therapy. Int J Rheum Dis 2021;24:254–259.

[28] Giannitti C, Lopalco G, Vitale A, Rigante D, Anelli MG, Fabbroni M, et al. Long-term safety of anti-TNF agents on the liver of patients with spondyloarthritis and potential occult hepatitis B viral infection: an observational multicentre study. Clin Exp Rheumatol 2017;35:93–97.

[29] Lee JM, Wei SC, Lee KM, Ye BD, Mao R, Kim HS, et al. Clinical course of hepatitis B viral infection in patients undergoing anti-tumor necrosis factor α therapy for inflammatory bowel disease. Gut Liver 2021.

[30] Mori S. Past hepatitis B virus infection in rheumatoid arthritis patients receiving biological and/or nonbiological disease-modifying antirheumatic drugs. Mod Rheumatol 2011;21:621–627.

[31] Nakamura J, Nagashima T, Nagatani K, Yoshio T, Iwamoto M, Minota S. Reactivation of hepatitis B virus in rheumatoid arthritis patients treated with biological disease-modifying antirheumatic drugs. Int J Rheum Dis 2016;19:470–475.

[32] Papa A, Felice C, Marzo M, Andrisani G, Armuzzi A, Covino M, et al. Prevalence and natural history of hepatitis B and C infections in a large population of IBD patients treated with anti-tumor necrosis factor-α agents. J Crohns Colitis 2013;7:113–119.

[33] Papalopoulos I, Fanouriakis A, Kougkas N, Flouri I, Sourvinos G, Bertsias G, et al. Liver safety of non-tumour necrosis factor inhibitors in rheumatic patients with past hepatitis B virus infection: an observational, controlled, long-term study. Clin Exp Rheumatol 2018;36:102–109.

[34] Pauly MP, Tucker LY, Szpakowski JL, Ready JB, Baer D, Hwang J, et al. Incidence of hepatitis B virus reactivation and hepatotoxicity in patients receiving long-term treatment with tumor necrosis factor Antagonists. Clin Gastroenterol Hepatol 2018;16:1964–1973.e1.

[35] Solay AH, Acar A, Eser F, Kuşco F, Tütüncü EE, Kul G, et al. Reactivation rates in patients using biological agents, with resolved HBV infection or isolated anti-HBc IgG positivity. Turkish J Gastroenterol 2018;29:561–565.

[36] Tamori A, Koike T, Goto H, Wakitani S, Tada M, Morikawa H, et al. Prospective study of reactivation of hepatitis B virus in patients with rheumatoid arthritis who received immunosuppressive therapy: evaluation of both HBsAg-positive and HBsAg-negative cohorts. J Gastroenterol 2011;46:556–564.

[37] Ye H, Zhang XW, Mu R, Fang LK, Gu JR, Lin J, et al. Anti-TNF therapy in patients with HBV infection-analysis of 87 patients with inflammatory arthritis. Clin Rheumatol 2014;33:119–123.

[38] Byeon S, Cho JH, Jung HA, Sun JM, Lee SH, Ahn JS, et al. PD-1 inhibitors for non-small cell lung cancer patients with special issues: real-world evidence. Cancer Med 2020;9:2352–2362.

[39] Chan GH, Gwee YX, Low JL, Huang Y, Chan ZY, Choo JR, et al. Immune checkpoint inhibition for non-small cell lung cancer in patients with pulmonary tuberculosis or Hepatitis B: experience from a single Asian centre. Lung Cancer 2020;146:145–153.

[40] Lee PC, Chao Y, Chen MH, Lan KH, Lee IC, Hou MC, et al. Risk of HBV reactivation in patients with immune checkpoint inhibitor-treated unresectable hepatocellular carcinoma. J ImmunoTherapy Cancer 2020;8.

[41] Ng KYY, Wong LWJ, Ang AJS, Tan SH, Choo SP, Tai DW, et al. Real-world efficacy and safety of immune checkpoint inhibitors in advanced hepatocellular carcinoma: experience of a tertiary Asian Center. Asia Pac J Clin Oncol 2020.

[42] Pertejo-Fernandez A, Ricciuti B, Hammond SP, Marty FM, Recondo G, Rangachari D, et al. Safety and efficacy of immune checkpoint inhibitors in patients with non-small cell lung cancer and hepatitis B or hepatitis C infection. Lung Cancer 2020;145:181–185.

[43] Shah NJ, Al-Shbool G, Blackburn M, Cook M, Belouali A, Liu SV, et al. Safety and efficacy of immune checkpoint inhibitors (ICIs) in cancer patients with HIV, hepatitis B, or hepatitis C viral infection. J Immunother Cancer 2019;7:353.

[44] Wong GL, Wong VW, Hui VW, Yip TC, Tse YK, Liang LY, et al. Hepatitis flare during immunotherapy in patients with current or past hepatitis B virus infection. Am J Gastroenterol 2021;116:1274–1283.

[45] Yoo S, Lee D, Shim JH, Kim KM, Lim YS, Lee HC, et al. Risk of hepatitis B virus reactivation in patients treated with immunotherapy for anti-cancer treatment. Clin Gastroenterol Hepatol 2021.

[46] Orlandi EM, Elena C, Bono E. Risk of hepatitis B reactivation under treatment with tyrosine-kinase inhibitors for chronic myeloid leukemia. Leuk Lymphoma 2017;58:1764–1766.

[47] Sorà F, Ponziani FR, Laurenti L, Chiusolo P, Autore F, Gasbarrini A, et al. Low risk of hepatitis B virus reactivation in patients with resolved infection and chronic myeloid leukemia treated with tyrosine kinase inhibitors. Leuk Lymphoma 2017;58:993–995.

[48] Wang YH, Liang JD, Sheng WH, Tien FM, Chen CY, Tien HF. Hepatitis B reactivation during treatment of tyrosine kinase inhibitors-Experience in 142 adult patients with chronic myeloid leukemia. Leuk Res 2019;81:95–97.

[49] Yao ZH, Liao WY, Ho CC, Chen KY, Shih JY, Chen JS, et al. Incidence of hepatitis B reactivation during epidermal growth factor receptor tyrosine kinase inhibitor treatment in non–small-cell lung cancer patients. Eur J Cancer 2019;117:107–115.

[50] Ahn SS, Jung SM, Song JJ, Park YB, Park JY, Lee SW. Safety of tocilizumab in rheumatoid arthritis patients with resolved hepatitis B virus infection: data from real-world experience. Yonsei Med J 2018;59:452–456.

[51] Chen YM, Chen HH, Huang WN, Chen YH, Hsieh TY, Yang SS, et al. Reactivation of hepatitis B virus infection following rituximab treatment in HBsAg-negative, HBcAb-positive rheumatoid arthritis patients: a long-term, real-world observation. Int J Rheum Dis 2019;22:1145–1151.

[52] Chiu HY, Chen CH, Wu MS, Cheng YP, Tsai TF. The safety profile of ustekinumab in the treatment of patients with psoriasis and concurrent hepatitis B or C. Br J Dermatol 2013;169:1295–1303.

[53] Chiu HY, Hui RCY, Huang YH, Huang RY, Chen KL, Tsai YC, et al. Safety profile of secukinumab in treatment of patients with psoriasis and concurrent hepatitis B or C: a multicentric prospective cohort study. Acta Dermato-Venereologica 2018;98:829–834.

[54] Kuo MH, Tseng CW, Lu MC, Tung CH, Tseng KC, Huang KY, et al. Risk of hepatitis B reactivation in rheumatoid arthritis patients undergoing tocilizumab-containing treatment. Dig Dis Sci 2021.

[55] Lin CT, Huang WN, Hsieh CW, Chen YM, Chen DY, Hsieh TY, et al. Safety and effectiveness of tocilizumab in treating patients with rheumatoid arthritis - a three-year study in Taiwan. J Microbiol Immunol Infect 2019;52:141–150.

[56] Rodríguez-Tajes S, Miralpeix A, Costa J, López-Suñé E, Laguno M, Pocurull A, et al. Low risk of hepatitis B reactivation in patients with severe COVID-19 who receive immunosuppressive therapy. J Viral Hepat 2021;28:89–94.

[57] Ting SW, Chen YC, Huang YH. Risk of hepatitis B reactivation in patients with psoriasis on ustekinumab. Clin Drug Invest 2018;38:873–880.

[58] Kim PS, Ho GY, Prete PE, Furst DE. Safety and efficacy of abatacept in eight rheumatoid arthritis patients with chronic hepatitis B. Arthritis Care Res 2012;64:1265–1268.

[59] Padovan M, Filippini M, Tincani A, Lanciano E, Bruschi E, Epis O, et al. Safety of abatacept in rheumatoid arthritis with serologic evidence of past or present hepatitis B virus infection. Arthritis Care Res 2016;68:738–743.

[60] Zappulo E, Nicolini LA, Di Grazia C, Dominietto A, Lamparelli T, Gualandi F, et al. Efficacy of lamivudine prophylaxis in preventing hepatitis B virus reactivation in patients with resolved infection undergoing allogeneic SCT and receiving rituximab. Infection 2019;47:59–65.

[61] **Cao W**, **Wei J**, Wang N, Xu H, Xiao M, Huang L, et al. Entecavir prophylaxis for hepatitis B virus reactivation in patients with CAR T-cell therapy. Blood 2020;136:516–519.

[62] Cui R, Lyu C, Li Q, Jiang Y, Mou N, Yang Z, et al. Humanized anti-CD19 chimeric antigen receptor-T cell therapy is safe and effective in lymphoma and leukemia patients with chronic and resolved hepatitis B virus infection. Hematol Oncol 2021;39:75–86.

[63] **Li P**, **Zhou L**, **Ye S**, Zhang W, Wang J, Tang X, et al. Risk of HBV reactivation in patients with resolved HBV infection receiving anti-CD19 chimeric antigen receptor T cell therapy without antiviral prophylaxis. Front Immunol 2021;12:638678.

[64] Liu W, Huang W, Wang M, Lv R, Li J, Wang Y, et al. Risk of hepatitis B reactivation is controllable in patients with B-cell lymphoma receiving anti-CD19 CAR T cell therapy. Br J Haematol 2020;191:126–129.

[65] **Wang Y**, **Liu Y**, **Tan X**, Pan B, Ge J, Qi K, et al. Safety and efficacy of chimeric antigen receptor (CAR)-T-cell therapy in persons with advanced B-cell cancers and hepatitis B virus-infection. Leukemia 2020;34:2704–2707.

[66] **Yang C**, **Xie M**, Zhang K, Liu H, Liang A, Young KH, et al. Risk of HBV reactivation post CD19-CAR-T cell therapy in DLBCL patients with concomitant chronic HBV infection. Leukemia 2020;34:3055–3059.

[67] Hatano M, Mimura T, Shimada A, Noda M, Katayama S. Hepatitis B virus reactivation with corticosteroid therapy in patients with adrenal insufficiency. Endocrinol Diabetes Metab 2019;2:e00071.

[68] Kim TW, Kim MN, Kwon JW, Kim KM, Kim SH, Kim W, et al. Risk of hepatitis B virus reactivation in patients with asthma or chronic obstructive pulmonary disease treated with corticosteroids. Respirology 2010;15:1092–1097.

[69] Notsumata K, Nomura Y, Tanaka A, Nomura Y, Ueda T, Sanada T, et al. Efficient prophylactic management of HBV reactivation by an information technology encoding system: results of a 6-year prospective cohort study. Intern Med 2020;59:2457–2464.

[70] Wong GL, Wong VW, Yuen BW, Tse YK, Yip TC, Luk HW, et al. Risk of hepatitis B surface antigen seroreversion after corticosteroid treatment in patients with previous hepatitis B virus exposure. J Hepatol 2020;72:57–66.

[71] Yang SS, Hung CT, Li SF, Lee HM, Chung YC, Chen HH, et al. Hepatitis B virus-related mortality in rheumatoid arthritis patients undergoing long-term low-dose glucocorticoid treatment: a population-based study. J Formos Med Assoc 2018;117:566–571.

[72] Chen MH, Chen MH, Liu CY, Tsai CY, Huang DF, Lin HY, et al. Hepatitis B virus reactivation in rheumatoid arthritis patients undergoing biologics treatment. J Infect Dis 2017;215:566–573.

[73] Karaca M, Tural D, Akar E, Çil I, Bayrak S, Ozet G, et al. Hepatitis B reactivation rate is higher undergoing some cytotoxic chemotherapy in patients with solid tumors: a large retrospective study. Chemotherapy 2019;63:247–252.

[74] Watanabe M, Shibuya A, Takada J, Tanaka Y, Minamino T, Okuwaki Y, et al. Entecavir can reduce the incidence and severity of hepatitis B virus reactivation. Hepatol Res 2010;40:728.

[75] Chen M, Zhuang J, Zhou D, Xu Y, Zhao Y, Wang S, et al. Outcome of anti-thymocyte immunoglobulin plus cyclosporine A for severe aplastic anaemia with chronic hepatitis B virus infection. Ann Hematol 2017;96:581–587.

[76] Mikulska M, Nicolini L, Signori A, Rivoli G, Del Bono V, Raiola AM, et al. Hepatitis B reactivation in HBsAg-negative/HBcAb-positive allogeneic haematopoietic stem cell transplant recipients: risk factors and outcome. Clin Microbiol Infect 2014;20:O694–O701.

[77] Shiah HS, Chen CY, Dai CY, Hsiao CF, Lin YJ, Su WC, et al. Randomised clinical trial: comparison of two everolimus dosing schedules in patients with advanced hepatocellular carcinoma. Aliment Pharmacol Ther 2013;37:62–73.

[78] Harigai M, Winthrop K, Takeuchi T, Hsieh TY, Chen YM, Smolen JS, et al. Evaluation of hepatitis B virus in clinical trials of baricitinib in rheumatoid arthritis. RMD Open 2020;6.

[79] **Cao X**, **Wang Y**, Li P, Huang W, Lu X, Lu H. HBV reactivation during the treatment of non-hodgkin lymphoma and management strategies. Front Oncol 2021;11:685706.

[80] Evens AM, Jovanovic BD, Su YC, Raisch DW, Ganger D, Belknap SM, et al. Rituximab-associated hepatitis B virus (HBV) reactivation in lympho-proliferative diseases: meta-analysis and examination of FDA safety reports. Ann Oncol 2011;22:1170–1180.

[81] Varisco V, Vigano M, Batticciotto A, Lampertico P, Marchesoni A, Gibertini P, et al. Low risk of hepatitis B virus reactivation in HBsAg-negative/anti-HBc-positive carriers receiving rituximab for rheumatoid arthritis: a retrospective multicenter Italian study. J Rheumatol 2016;43:869–874.

[82] Fraenkel L, Bathon JM, England BR, St. Clair EW, Arayassi T, Carandang K, et al. 2021 American College of Rheumatology Guideline for the treatment of rheumatoid arthritis. Arthritis Care Res (Hoboken) 2021;73:924–939.

[83] Hwang JP, Lok AS, Fisch MJ, Cantor SB, Barbo A, Lin HY, et al. Models to predict hepatitis B virus infection among patients with cancer undergoing systemic anticancer therapy: a prospective cohort study. J Clin Oncol 2018;36:959–967.

[84] Arora A, Anand AC, Kumar A, Singh SP, Aggarwal R, Dhiman RK, et al. INASL guidelines on management of hepatitis B virus infection in patients receiving chemotherapy, biologicals, immunosupressants, or corticosteroids. J Clin Exp Hepatol 2018;8:403–431.

[85] **Jiang HY**, **Wang SY**, Deng M, Li YC, Ling ZX, Shao L, et al. Immune response to hepatitis B vaccination among people with inflammatory bowel diseases: a systematic review and meta-analysis. Vaccine 2017;35:2633–2641.

[86] Cholongitas E, Haidich AB, Apostolidou-Kiouti F, Chalevas P, Papatheodoridis GV. Hepatitis B virus reactivation in HBsAg-negative, anti-HBc-positive patients receiving immunosuppressive therapy: a systematic review. Ann Gastroenterol 2018;31:480–490.