

Hepatitis B Virus Reactivation in Cancer Patients Treated With Immune Checkpoint Inhibitors

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Summary: There have been unique adverse events reported with targeted blockade of programmed death-1 (PD-1), programmed death-ligand-1 (PD-L1), and cytotoxic T-lymphocyte-associated protein-4 (CTLA4), including immune mediated toxicities. Recently, there have been reports of hepatitis B reactivation (HBVr) occurring with PD-1/PD-L1 inhibitors, which may result in treatment delays, interruptions, or discontinuation. This retrospective literature review and analysis of the Food and Drug Administration's (FDA) Adverse Events Reporting System (FAERS) queried reported cases of "Hepatitis B reactivation" reported with the PD-1/PD-L1 inhibitors "Pembrolizumab," "Atezolizumab," "Nivolumab," "Durvalumab," "Avelumab," and "Ipilimumab" from initial FDA approval to June 30, 2020. Disproportionality signal analysis was determined by calculating a reporting odds ratio (ROR) and 95% confidence intervals (CI). The ROR was considered significant when the lower and upper limits of the 95% CI were > 1 and confirmed by the Fisher exact test ($P < 0.05$). Pembrolizumab had a strong signal associated with HBVr, with a ROR of 2.32 (95% CI: 1.11–4.28) ($P = 0.013$) and was the only statistically significant finding. There were no reports of HBVr with Ipilimumab or Avelumab. Additional prospective studies should be conducted to validate the findings of this retrospective pharmacovigilance analysis to determine the risk of HBVr in patients receiving immune checkpoint inhibitors.

Key Words: hepatitis B reactivation, chronic hepatitis B, cancer, immunotherapy, immune check point inhibitor, programmed death-1, programmed death-ligand-1, Pembrolizumab

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Chronic hepatitis B infection (HBV) is a major cause of morbidity and mortality worldwide, with 257 million individuals infected in 2015.¹ HBV reactivation (HBVr) while uncommon, is well described in cancer patients, and pretreatment HBV screening is routinely recommended for patients that require cytotoxic chemotherapy and immunosuppressive agents such as rituximab.²

In addition to the direct effect of HBVr on morbidity and mortality in the general population, HBVr poses unique challenges to the oncologic population including the possibility of treatment delays or discontinuation of systemic therapies that may affect overall survival.

There are reports of HBVr occurring in patients treated with programmed death-1 (PD-1) and programmed death-ligand-1 (PD-L1) immune checkpoint inhibitor (ICI) therapy. These monoclonal antibodies disrupt the interaction between PD-1 (Nivolumab and Pembrolizumab), PD-L1 (Durvalumab, Atezolizumab, Avelumab), and cytotoxic T-lymphocyte-associated protein-4 (CTLA4) (Ipilimumab), which enhances the T-lymphocyte response and potentiates the immune mediated destruction of malignant cells.³ There is also evidence to suggest that PD-1/PD-L1 blockade enhances the immune mediated elimination of both acute and chronic viral infections, although data is conflicting.^{4,5} Rat models with an enhanced immune response through PD-1 blockade have demonstrated improved viral clearance in both acute and chronic infections, whereas ex vivo studies have suggested a heterogenous cytotoxic T-lymphocyte response with intermediate T-lymphocyte differentiation in response to chronic HBV.^{6,7} In addition, over activation of the immune response in patients receiving PD-1/PD-L1 immunotherapy has been linked to tissue damage through immune mediated adverse effects (AEs), including hepatic inflammation and acute liver failure.⁸ Consequently, the relationship between PD-1/PD-L1 inhibitors and immune mediated clearance of chronic infections such as HBV in the oncologic population has not been sufficiently validated.

In many of the pivotal trials utilizing PD-1/PD-L1 inhibitors for solid tumors, patients with chronic HBV were excluded from enrollment or included if they had low viral loads and were on prophylactic antiviral therapy before immunotherapy initiation. Therefore, the association of HBVr with PD-1/PD-L1 immunotherapy is not clearly established. In the present study, we retrospectively reviewed the pharmacovigilance US Food and Drug Administration (FDA) Adverse Events Reporting System (FAERS) database for the development of HBVr reported with PD-1/PD-L1 inhibitors and conducted a systematic literature review on all reports in the literature.

METHODS

FDA FAERS

FAERS is a public pharmacovigilance database that was created by FDA and includes adverse events reported

by patients, health care providers, or pharmaceutical manufacturing companies in both study populations and the clinical care setting. FAERS is evaluated by clinical reviewers in the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research.⁹ As of December 2019, over 19 million individual adverse cases were reported to FAERS, making it a valuable resource for postmarketing data, clinical inference, and hypothesis generation. Data in FAERS includes an identification number, demographic data (age, sex, height, weight), the date the reported event occurred, suspected causative medication, AE severity (serious or nonserious), outcomes (hospitalized, death, other outcomes), other concomitant medications, country of AE, pharmaceutical company, reporter (patient, provider or manufacturing/pharmaceutical company, unknown),¹⁰ and the literature reference if the case was published.¹⁰

FAERS Data Collection and Statistical Analysis

This was a retrospective review utilizing the FAERS pharmacovigilance database and a systematic literature search for all cases of HBVr reported with the PD-1/PD-L1 inhibitors from year of first FDA approval through March 31, 2020 (last accessed: March 31, 2020). FAERS was queried for “Hepatitis B reactivation” that was reported as an AE occurring with “Pembrolizumab,” “Atezolizumab,” “Nivolumab,” “Durvalumab,” and “Avelumab.” The total number of HBVr and total number of reported AE were collected with each immunotherapy in which ≥ 1 report of HBVr was recorded. Each HBVr report with PD-1/PD-L1 inhibitors was collected and exported into a Microsoft excel 2013 document. If there were no HBVr reported with an ICI, it was excluded from further analysis. In addition, the total number of reported HBVr as well as the cumulative number of AE reported in FAERS starting from earliest FDA approval documented for the immunotherapy agents was determined. Additional data collected for analysis included median age (range), indication for use, sex (male/female/unknown), country and geographic endemic risk,^{11,12} outcome (hospitalization/life-threatening/death/other) and if the patient event was previously published.

Descriptive statistics were reported as median with ranges for continuous variables and as frequencies and percentages for categorical variables. Disproportionality signal analysis was conducted to assess the magnitude of association between HBVr and PD/PD-L1 inhibitors compared with all reported events in FAERS through the reporting odds ratio (ROR) and associated 95% confidence intervals (CI). The magnitude of ROR (> or <1) determined the direction of association. Results were considered statistically significant if the lower limit of the 95% CI did not cross 1 and associated the Fisher exact test had an associated 2-sided *P*-value of <0.05. The method of

calculating the ROR and 95% CI which was reported in a previous pharmacovigilance analysis of FAERS is listed as follows.¹⁰

	PD-1/PD-L1 Inhibitor	All Other Medications	Sum
HBVr	A	B	A+B
All other events	C	D	C+D
Sum	A+C	B+D	A+B+C+D

$$ROR: A \times D / B \times C$$

$$CI: e^{(\ln ROR \pm 1.96s)}$$

$$\text{Where } s = \text{standard deviation} = \sqrt{(1/A + 1/B + 1/C + 1/D)}$$

All analyses were performed with STATA version 16 (StataCorp. 2019. Stata Statistical Software: Release 16; StataCorp LLC, College Station, TX).

Systematic Review

A database search was performed using Boolean logic with terms including medications’ both generic and brand name, in combination with terms related to hepatitis B (including HBVr, chronic hepatitis B virus, and acute hepatitis B). Medical Subject Headings (MeSH) terminology was used, and terms were searched as keywords. The following databases were used: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process and Other Non-Indexed Citations, Daily and Versions(R) from inception to March 31, 2020. In addition, google scholar was screened for any additional outlying publications including published abstracts. Similar data to the FAERS data collection and statistical analysis section was collected, with the addition of viral load, antiviral prophylaxis and treatment, time from checkpoint therapy initiation to reported HBVr, time from infection diagnosis to undetectable viral load, and the effect this had on cancer treatment. This data was not available in FAERS. In addition, case reports that are already included in FAERS database were identified.

RESULTS

FAERS Analysis

Between January 1, 2014, and June 30, 2020, there were 11,891,488 individual AE reports within FAERS. Of these, 77,603 (0.65%) events were because of ICIs; 22,914 (0.18%) events reported with Pembrolizumab, 44,862 (0.38%) with Nivolumab, 7677 (0.06%) with Atezolizumab, and 3150 (0.03%) with Durvalumab. There were no reports of HBVr with Ipilimumab or Avelumab, so they were excluded from further analysis. There was a total of 2335 (0.02%) reports of HBVr in FAERS. Of the reports of HBVr, 22 (0.90%) were reported with PD-1/PD-L1 inhibitors; 10 (0.43%) with Pembrolizumab,

TABLE 1. Number of Patients With Documented HBVr Since Initial FDA Approval of Each Drug, Total Reported HBVr in FAERS Database From Time of Earliest FDA Approval of Immunotherapy Agent, and total Number of Reported Cases in FAERS, 2014–2020

Therapy	Initial FDA Approval	HBVr with Therapy (n)/ Percent AE of Therapy	Total Number of Reported HBVr (n) in FAERS	Total Reported AE with Therapy	Total Number of Reported Events in FAERS
Total	2014–2020	22/0.03	2335	77,603	11,891,488
Pembrolizumab	2014–2020	10/0.04	2335	21,914	11,891,488
Nivolumab	2014–2020	7/0.01	2335	44,862	11,891,488
Atezolizumab	2016–2020	4/0.05	1940	7677	8,960,298
Durvalumab	2017–2020	1/0.03	1577	3150	7,268,785

AE indicates adverse effect; FAERS, FDA Adverse Events Reporting System; FDA, Food and Drug Administration; HBVr, hepatitis B reactivation.

TABLE 2. Summary of Association Between Immunotherapy (Pembrolizumab, Nivolumab, Atezolizumab, and a Summation of the 3) and HBVr, With Respect to all Cases Reported in FAERS From Initial FDA Approval to January 1, 2020

Therapy	ROR of Therapy vs. Full Database	95% CI	P
Total	1.44	0.90–2.19	0.093
Pembrolizumab	2.32	1.11–4.28	0.013
Nivolumab	0.79	0.32–1.64	0.73
Atezolizumab	2.41	0.65–6.18	0.088
Durvalumab	1.46	0.04–8.17	0.5
Pembrolizumab+ nivolumab	1.3	0.75–2.08	0.27
Atezolizumab+ durvalumab	2.13	0.69–4.99	0.089

P value was obtained from the Fisher exact test.

CI indicates confidence interval; FAERS, Food and Drug Administration Adverse Events Reporting System; FDA, Food and Drug Administration; HBVr, hepatitis B virus reactivation; ROR, reporting odds ratio.

7 (0.30%) with Nivolumab, 4 (0.17%) with Atezolizumab, and 1 (0.04%) with Durvalumab (Table 1). The magnitude of association of developing HBVr was significant for Pembrolizumab (ROR: 2.32, 95% CI: 1.11–4.28, $P=0.013$). The ROR for Atezolizumab (ROR: 2.41, 95% CI: 0.65–6.18, $P=0.088$), Nivolumab (ROR: 0.79, 95% CI: 0.35–1.82, $P=0.73$), and Durvalumab (ROR: 1.46, 95% CI: 0.04–8.17, $P=0.5$) was not significant. Furthermore, the total composite of all 4 ICIs (ROR: 1.44, 95% CI: 0.90–2.319, $P=0.093$), and the sum of HBVr occurring with Pembrolizumab+Nivolumab (ROR: 1.3, 95% CI: 0.75–2.8, $P=0.27$) and Atezolizumab+Durvalumab (ROR: 2.13, 95% CI: 0.69–4.99, $P=0.089$) were not statistically significant (Table 2, Fig. 1). There was a total of 11 (50.0%) males, 8 (36.4%) females, and 3 (13.6%) cases with unknown sex. A total of 4 (18.2%) cases of HBVr were reported by countries considered to be high-intermediate endemicity for HBV [prevalence of hepatitis B surface antigen (HBsAg) is 5.0% to 7.9%], and there were no reports from countries considered to have a high HBV endemicity (prevalence of HBsAg is 8% of greater). The most common indication for treatment was non-small cell lung cancer (NSCLC). The median age for all cases was 58 (36 to 83) years (Table 3). A total of 5 (22.7%) patients with HBVr died (Table 3).

Literature Review

Systematic literature review yielded 172 studies, of which 6 reported cases and one published abstract of HBVr were identified and included.^{13–17} Of the 7 reported cases, 6 (85.7%) patients were reported in FAERS and included in that analysis^{13,15–17} and 1 patient was not included in FAERS.¹⁴ There were 6 (85.7%) males and 1 (14.3%) female with an overall median age of 51 (36–72) years. Three (42.8%) were treated with Pembrolizumab, 2 (28.6%) for NSCLC and 1 (14.3%) for malignant melanoma.^{13,15,16} Time to HBVr was reported in one patient on Pembrolizumab which was 28 weeks, and that patient was known to have chronic HBV.¹³ One patient on Pembrolizumab received Tenofovir, 1 did not receive an antiviral, and antiviral coverage was not reported in 1 case report.^{13,15,16} Immunotherapy was delayed in 1 patient.¹⁵ Mean time for an undetectable viral load when reported was 7.5 weeks after diagnosis. Four (57.1%) patients reported in the literature received Nivolumab, 1 each for malignant melanoma, NSCLC, soft tissue sarcoma, and hepatocellular carcinoma (HCC).^{13,14,17} Time to HBVr after initiating therapy was reported in 2 patients, with a mean time to HBVr of 16 weeks. Two patients received Entecavir¹³ and 2 received Tenofovir^{14,17} for therapy. Three (75%) of these patients had a known history of hepatitis B.^{13,14} Immunotherapy was delayed¹⁷ in 1 patient and discontinued¹³ in 1 patient. Time to reach undetectable HBV viral load was reported in 2 patients,¹³ and mean time to achieve this was 4.5 weeks (Table 4).

DISCUSSION

The development of PD-1/PD-L1 ICIs has shown promising clinical responses in melanomas, lung cancers, lymphomas, and renal cancers overexpressing PD-L1, a mechanism that allows cancer cells to evade the T-lymphocyte immune response and allow unregulated proliferation.¹⁸ However, these therapies can result in unintended downstream consequences such as immune mediated adverse events.¹⁹ Although PD-1/PD-L1 inhibitors stimulate the T-lymphocyte immune response, drug-related infectious complications including HBVr have been reported.^{13–17} Data from this retrospective pharmacovigilance analysis suggests a significant association between Pembrolizumab and HBVr, but not with other PD-1/PD-L1 ICIs.

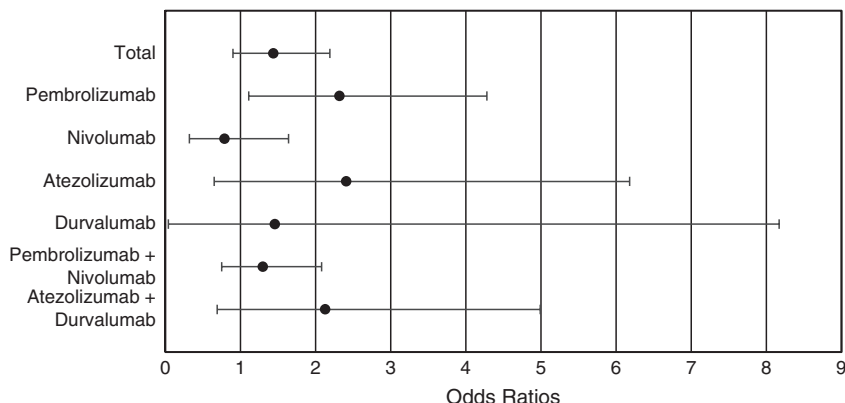


FIGURE 1. Forrest plot of reporting odds ratio in hepatitis B reactivation occurring with programmed death-1/programmed death-ligand-1 inhibitors with 95% confidence intervals.

TABLE 3. Patient Characteristics and Treatment Indications

	Pembrolizumab, n (%)	Nivolumab, n (%)	Atezolizumab, n (%)	Durvalumab, n (%)	Total, n (%)
Reports of HBVr	10	7	4	1	22
Sex					
Male	6 (60.0)	3 (42.8)	1 (25.0)	1	11 (50.0)
Female	3 (30.0)	2 (28.6)	3 (75.0)	0	8 (36.4)
Not reported	1 (10.0)	2 (28.6)	0	0	3 (13.6)
Median age (range)	51.0 (36–71)	45 (36–72)	83 (83)	67	58 (36–83)
Not reported	3 (30.0)	2 (28.6)	1 (25.0)	0	6 (27.3)
Reporter type					
Health care professional	10 (100)	7 (100.0)	4 (100.0)	1 (100.0)	22 (100.0)
Unknown	0	0	0	0	
Outcomes*					
Total	15	10	4	2	31
Hospitalization	3 (20.0)	1 (10.0)	0	1 (50.0)	5 (16.1)
Life-threatening	1 (6.7)	0	0	0	1 (3.2)
Death	1 (6.7)	3 (30.0)	0	1	5 (16.1)
Other	10 (66.7)	6 (60.0)	4 (100.0)	0	20 (64.5)
Concomitant medications					
PD-1/PD-L1	8 (80.0)	6 (85.7)	4 (100.0)	0	18 (81.9)
PD-1/PD-L1+1	0	1 (14.3)	0	0	1 (4.5)
PD-1/PD-L1+≥2	2 (20.0)	0	0	1 (100.0)	3 (13.6)
Country reported					
China†	1 (10.0)	2 (28.6)	0	0	3 (13.6)
Hong Kong†	0	0	1 (25.0)	0	1 (4.5)
USA‡	6 (60.0)	2 (28.6)	0	0	8 (36.4)
Hungary‡	0	1 (14.3)	0	0	1 (4.5)
South Korea‡	0	1 (14.3)	0	0	1 (4.5)
France‡	1 (10.0)	0	0	1 (100.0)	2 (9.1)
Bulgaria‡	2 (20.0)	0	0	0	2 (9.1)
Japan‡	0	1 (14.3)	0	0	1 (4.5)
Belgium‡	0	0	3 (75.0)	0	3 (13.6)
Reported in the literature?	4 (40.0)	4 (57.1)	0	0	8 (36.4)
Indication					
Transitional cell carcinoma	0	0	1 (25.0)	0	1 (4.5)
Soft tissue sarcoma	0	1 (14.3)	0	0	1 (4.5)
Hepatocellular carcinoma	0	2 (28.6)	0	0	2 (9.1)
Non-Hodgkin’s lymphoma	1 (10.0)	1 (14.3)	0	0	2 (9.1)
Hodgkin’s lymphoma	0	1 (14.3)	0	0	1 (4.5)
Malignant melanoma	2 (20.0)	1 (14.3)	0	0	3 (13.6)
Thymic carcinoma	1 (10.0)	0	0	0	1 (4.5)
Non-small cell carcinoma	3 (30.0)	0	0	1 (100.0)	4 (18.2)
Small Cell carcinoma	1 (10.0)	0	0	0	1 (4.5)
Unspecified lung cancer	0	1 (14.3)	0	0	1 (4.5)
Breast cancer	0	0	3 (75.0)	0	3 (13.6)
Malignancy type not reported	2 (20.0)	0	0	0	2 (9.1)

*More than one outcome may have been reported with each patient case.

†Countries that are considered to be high-intermediate (prevalence of HBsAg is 5.0% to 7.9%) endemicity.

‡Countries that are considered to have low to low-intermediate (<4.99% prevalence of HbsAg) endemicity.

HBsAg indicates hepatitis B surface antigen; HBVr, hepatitis B reactivation; PD-1, programmed death-1; PD-L1, programmed death-ligand-1.

In the United States, it is estimated that there are anywhere between 862,000 and 2.2 million adults living with chronic HBV.^{20,21} This becomes particularly relevant in oncologic and rheumatologic patients receiving chemotherapy, immunotherapy, or biological agents that may suppress the immune response in patients with chronic HBV status that have underlying risk factors for HBVr (Fig. S1, Supplemental Digital Content 1, <http://links.lww.com/JIT/A596>). HBVr occurring in the setting of cytotoxic chemotherapy and other immunosuppressive agents such as rituximab is well described. In general, the American Association for the Study of Liver Diseases (AASLD) recommends routine HBV screening and initiation of appropriate antiviral prophylaxis in any patient requiring immunosuppressive or cytotoxic chemotherapy,^{22,23} and provide recommended diagnostic criteria (Table S1, Supplemental Digital Content 2, <http://links.lww.com/JIT/A597>).²³ Whether

similar recommendations should be considered for the growing population of patients receiving ICIs has not been determined. In many clinical trials using PD-1/PD-L1 ICIs, patients with known HBV were excluded. In the few that did include HBV patients, such as the Checkmate-040 study assessing Nivolumab in patients with advanced HCC,²⁴ and the Keynote-224²⁵ study assessing the response of advanced HCC to Pembrolizumab, patients with pre-existing HBV were included if they were on antiviral prophylaxis before initiation of immunotherapy. No HBVr was reported in the Checkmate-040²⁴ study, although in a separate analysis of the Asian cohort, 9% to 11% of patients with HBV experienced a >1 log increase in HBV DNA from baseline levels.²⁶ No flares were reported in the Keynote-224 study, but HBVr was not specifically reported.²⁵ In a recent retrospective safety analysis of ICI therapy in 16 patients with known chronic HBV receiving PD-1/PD-L1 blockade, no

TABLE 4. Patient Characteristics From Literature Review

References	Age (Sex)	ICI/ Indication	Known HBV (HBV DNA)	Antiviral PPX	Time to HBVr in weeks (Viral DNA Load)	HBVr Serology (HBV)	Antiviral	Disruption in Therapy	Time to Undetectable Viral Load (wks)
Zhang et al ^{13*}	39 (M)	P/Melanoma	+ (-)	No	28 (2.10×10 ³)	NR	No	No	5
	36 (M)	N/HCC	+ (-)	No	12 (1.80×10 ³)	NR	ETV	Stopped	1
	41 (F)	N/Sarcoma	+ (-)	Yes	20 (6.00×10 ⁷)	NR	ETV	No	8
Koskal et al ¹⁴	56 (M)	N†/Melanoma	+ (-)	No	NR (2.44×10 ⁵)	sAg ⁺ sAb ⁻ cAb IgM ⁺ eAb ⁺	TDF	No	NR
	Lake et al ^{17*}	72 (M)	N/NSCLC	- (NA)	NA	~4 (> 1.70×10 ⁸)	eAg ⁻ sAg ⁺ eAg ⁺ eAb ⁻	TDF	Delayed
Ragunathan ^{16*}	51 (M)	P/NSCLC	- (NA)	NA	NR (> 8.23 log)	sAg ⁺ sAb ⁻ cIgG ⁺ cIgM ⁻	NR	NR	NR
Pandey et al ^{15*}	51 (M)	P/NSCLC	- (NA)	NA	NR (> 8.23 log)	sAg ⁺ sAb ⁻ cAbIgM ⁻ cAb IgG ⁺	TDF	Delayed	10
						eAg ⁻ eAb ⁺			

*Case was listed in FAERS and included in analysis.

†Was also receiving ipilimumab.

cAb indicates core antibody; eAb, envelope antibody; eAg, envelope antigen; ETV, Entecavir; F, female; HBVr, hepatitis B virus reactivation; HCC, hepatocellular carcinoma; ICP, immune checkpoint inhibitors; M, male; N, nivolumab; NR, not reported; NSCLC, non-small cell lung cancer; P, pembrolizumab; PPX, prophylaxis; sAb, surface antibody; sAg, surface antigen; TDF, tenofovir.

reactivations occurred, and viral load in available patients did not change after starting therapy.²⁷ In a single institution retrospective study in China, Zhang et al¹³ found that out of the 114 patients receiving immunotherapy with a known history of HBV, 6 (5.3%) developed HBVr, all of which had previously undetectable circulating levels of viral DNA. Among this cohort, lack of antiviral prophylaxis in patients with known history of HBV was the only significant risk for HBVr.¹³ In the current literature review, 4 of 7 patients had a known history of HBV before immunotherapy initiation.^{13,14} However, it should be noted that in the majority of case reports/series or retrospective studies, baseline HBV data (eg, HBV DNA) were not reported. These baseline factors might help to stratify patients according to their risk of reactivation. Stratifying patients would help clarify the effect of immune checkpoints in patients with low versus high viral loads. In addition to the level of HBV DNA copies, other important factors include baseline liver function tests and antibodies/antigen testing (mainly HBeAg).²⁸ Given this conflicting data, additional studies should be conducted to validate the risk reported in the present study.

In contrast to recent reports of ICIs resulting in HBVr, other data has indicated a possible therapeutic link between PD-1/PD-L1 blockade and the management of chronic viral infections. Data indicates that the PD-1/PD-L1 axis regulates the scale, quality, and duration of the T-cell response to infections.^{5,18} Binding of the T-cell's PD-1 surface receptor to PD-L1, or PD-L1 expressed on T cells to the B7 family of receptor molecules on antigen presenting cells results in T-cell inactivation. During chronic infections, viral infected cells have an array of immunosuppressive mechanisms resulting in incomplete viral elimination and resultant T-lymphocyte exhaustion.^{5,29} Sustained elevation of PD-1 is characteristically seen in an exhausted T-cell state.^{5,30} Conversely, inhibition of the PD-1/PD-L1 axis has been shown to reinvigorate the T-cell response in early chronic infection and reduce the viral load.^{5,31,32} Mouse models with chronic HBV and PD-1 blockade have demonstrated accelerated activation of intrahepatic T lymphocytes, in vivo viral clearance, and have suggested reduction in chronic viral persistence.^{28,33} Further corroborating this, a recent pilot study using Nivolumab in virally suppressed HBeAg negative patients with chronic HBV demonstrated a significant reduction in HBsAg from baseline,³⁴ indicating a possible antiviral therapeutic role.

Given this potential benefit, it would be counterintuitive for patients on PD-1/PD-L1 inhibitors to develop HBVr. However, it is possible that cancer patients with pre-existing risk factors with the addition of PD-1/PD-L1 therapy are more uniquely inclined to develop HBVr. Host factors such as male sex, age above 50 years, immunosuppressive diseases or medications, underlying cirrhosis, and virologic factors including baseline HBV DNA level or presence of HBV e antigen are more likely to develop HBVr (Fig. S1, Supplemental Digital Content 1, <http://links.lww.com/JIT/A596>).^{28,35} Severe infections in patients on PD-1/PD-L1 ICI are well known. Pneumonia because of opportunistic pathogens, herpes zoster, fungal infections, and sepsis have been reported in the CheckMate 063, KEYNOTE 010, and IMvigor 210 studies.³⁶⁻³⁸ There has been a report of CTLA4 inhibitor Ipilimumab associated with pulmonary aspergillosis pneumonia.³⁹ In addition, there are isolated reports of *Mycobacterium tuberculosis* reactivation⁴⁰⁻⁴⁶ with theorized mechanisms related to either drug-related lymphopenia, or unmasking of an underlying infection in an immune reconstitution inflammatory-like syndrome not dissimilar to what is seen in patients infected with human

immunodeficiency virus with rapid restoration of CD4 counts after initiation of antiretroviral therapy.^{39,44,45} In the setting of chronic HBV, immune reconstitution syndrome occurring in association with HIV is well described.⁴⁷⁻⁴⁹ It is possible a similar mechanism resulted in HBVr in these patients. Another possibility is that an accelerated immune response enhances tissue damage of hepatocytes and leads to release of viral particles that are not destroyed by circulating T lymphocytes either because of lymphopenia or because of an inadequate cytotoxic response.

This study was a retrospective, observational pharmacovigilance review and as such has limitations. This analysis does not predict the incidence of HBVr since FAERS does not contain a comprehensive list of every event that has occurred. While the utilization of pharmacovigilance databases to calculate the magnitude of association between a drug and adverse event occurring have been reported in other studies^{10,50} the ROR in both the present study and other analyses may be similarly limited. In addition, unless the case was published in the literature, baseline HBV status, patient characteristics including serology, antiviral use, and timeline to event occurrence was not available. Confounding variables such as concomitant immunosuppression, prior chemotherapy, or medication dosages were not reported in FAERS and these may have been contributory factors to reactivation. In addition, other factors, including the general adverse events profile of specific medications and the number of reported events may have affected the calculated ROR in this study. FAERS analysis, in contrast to other studies, compare the event rate to other events rather than the number of patients using the medication, which limits the data to predicting the magnitude of association rather than the true incidence. Moreover, population-specific factors, including primary disease, general physical performance, and prevalent comorbidities, might affect the final results.

While there may be an association between Pembrolizumab and HBVr, it appears to be a numerically uncommon occurrence and should be corroborated in additional prospective or post-marketing surveillance studies. Further retrospective real-world studies and prospective analyses should be conducted in endemic and nonendemic regions to validate the risk found in this study and to assess the need for HBV serologic testing and prophylactic antiviral therapy in patients before initiation of PD-1/PD-L1 ICIs.

CONCLUSION

Treatment with PD-1 and PD-L1 inhibitors have led to improved outcomes in patients with certain subsets of cancers. As the utilization of this therapy increases, it is important to identify and reduce the frequency of potential contributors that affect morbidity and mortality. In this study, Pembrolizumab had an increased association with HBVr, but this was not seen with other ICIs. Future prospective studies should further explore the association of HBVr and PD-1/PD-L1 based ICIs.

CONFLICTS OF INTEREST/FINANCIAL DISCLOSURES

None reported. All authors have declared there are no financial conflicts of interest with regard to this work.

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