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BRIEF REPORT

Reactivation of Resolved Hepatitis B After Daratumumab for Multiple Myeloma

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The risk of reactivation of resolved hepatitis B virus (HBV) in hepatitis B surface antigen (HBsAg)-negative multiple myeloma patients after daratumumab has not been reported. Among 93 patients with daratumumab treatment, reactivation occurred in 6 patients (6.5%) with one hepatic failure. This is the first report demonstrating a considerable risk of reactivation of resolved HBV after daratumumab.

Keywords. Daratumumab; hepatitis B virus; reactivation; multiple myeloma.

Daratumumab is a human immunoglobulin G1 monoclonal antibody targeting CD38-expressing cells [1]. Recently, several daratumumab-based combinations have shown promise in the treatment of newly diagnosed and refractory/relapsed multiple myeloma (MM) [2]. The principal mechanism of daratumumab to treat MM is inducing death of CD38-expressing myeloma cells through complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, and antibody-dependent cellular phagocytosis [1, 3]. Moreover, daratumumab was also shown to deplete CD38-expressing immune regulatory cells and may enhance the functionality of tumor-specific T cells in MM patients [3]. However, daratumumab also targets CD38-expressing normal plasma cells, which may cause the loss of protective immunity against viral infection including hepatitis B virus (HBV), leading to the reactivation of resolved infection [1, 4]. However, the risk of the reactivation of resolved HBV infection in hepatitis B surface antigen (HBsAg)-negative patients after daratumumab administration has not been reported. In this report, using the biggest single-center cohort in Korea, we describe the frequency and clinical characteristics of the reactivation of resolved HBV infection after daratumumab treatment in MM patients.

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Abbreviations: MM, multiple myeloma; anti-HBc, anti-hepatitis B core; TDF, tenofovir disoproxil fumarate

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METHODS

Study Population

From November 2014 to November 2020, 105 consecutive patients with MM were treated with daratumumab at Seoul St. Mary's Hospital. Of these patients, 12 patients were excluded (concomitant lymphoma [n = 1], HBsAg-positivity [n = 9], and follow-up less than 1 month [n = 2]). Finally, 93 HBsAg-negative patients were included and evaluated for the incidence of reactivation of resolved HBV infection. This study was approved by the Institutional Review Board of Seoul St. Mary's Hospital (KC21ZISI0060) and conducted following the Declaration of Helsinki.

Definition of HBV Reactivation in Patients With Resolved Infection

During follow-up, liver function tests were checked every month, and HBsAg/Ab with or without HBV DNA levels were checked every 6 months. Reactivation of resolved HBV infection was defined as HBsAg seroreversion or detection of HBV DNA (≥10 IU/mL) in initially HBsAg-negative patients [5, 6]. Among patients with reactivation of resolved HBV infection, severe hepatitis was defined when the levels of aspartate aminotransferase or alanine aminotransferase were increased more than five times of upper limit of normal (>200 mg/dL) [5]. When the reactivation of resolved HBV infection was diagnosed, patients with reactivation were treated with potent antiviral treatment including tenofovir disoproxil fumarate (TDF) and entecavir [5].

RESULTS

All the enrolled patients were relapsed/refractory MM treated with salvage daratumumab-based therapy (n = 76, monotherapy; n = 17, combination therapy). Among 93 HBsAg (–) patients enrolled in our study, 49 (52.7%) patients were HBsAb (+). Baseline anti-HBc was evaluated in 61 patients (65.6%), and 24 (39.3%) were anti-HBc (+) (Supplementary Figure 1). During the median follow-up period of 8.7 months (interquartile range, 4.1–16.0 months), reactivation of resolved infection occurred in 6 patients (6.5%) at the median of 8.5 months (1–26 months) after starting daratumumab (Table 1). All of the patients with reactivation received daratumumab monotherapy. Of the 6 patients with HBV reactivation, 4 patients showed HBsAb positivity (>10 IU/L) before treatment. At the time HBV reactivation was diagnosed, the median number of

Table 1. Clinical Characteristics of Patients With Reactivation of Resolved Hepatitis B Virus (HBV) Infection

	Baseline Characteristics									Laboratory Data at the Time When Patients Were Diagnosed With HBV Reactivation															
	Age	Sex	Prior HSCT	Tx.	HBsAg	HBsAb (IU/L)	anti-HBc (S/CO)	HCV Ab	Underlying Liver Disease	WBC ($x10^3$/uL)	Hemoglobin (g/dL)	Platelet ($x10^3$/uL)	Total Protein (g/dL)	Albumin (g/dL)	Total Bilirubin (mg/dL)	AST (mg/dL)	ALT (mg/dL)	INR	HBsAg	HBsAb (IU/L)	HBV DNA (log IU/mL)	Daratumumab Cycles Until the Reactivation	Duration From Daratumumab Start to Reactivation (months)	Antiviral Agent	Survival	Cause of Death
Patients 1	70	Male	–	Mono	–	475.9	Unchecked	–	–	5.14	11.3	128	9.4	3.4	7.2	2838	768	1.25	+	29.4	8	5	26	TDF	Survived	–
Patients 2	69	Male	–	Mono	–	2.0	Unchecked	–	–	3.84	9.4	5	8.5	2	7.06	283	310	1.92	+	2.0	6.3	2	2	TDF	Expired	Hepatic failure
Patients 3	71	Male	–	Mono	–	3.8	0.1	–	–	4.00	12	192	6.3	4.2	0.43	19	13	1.01	+	2.0	8.2	18	18	ETV	Survived	–
Patients 4	60	Male	–	Mono	–	93.54	2.83	–	–	7.80	9.8	104	5.9	3.6	0.45	34	37	1.02	+	2.0	7.5	3	8	ETV	Survived	–
Patients 5	58	Male	+	Mono	–	98.74	4.32	–	–	7.81	9.3	58	6.8	4	0.6	83	89	1.05	+	25.3	6.4	2	9	ETV	Expired	Myeloma progression
Patients 6	57	Male	+	Mono	–	25.3	3.06	–	–	3.53	11.0	51	5.6	3.4	0.44	18	13	0.97	+	2.0	4.6	1	1	ETV	Survived	–

Abbreviations: ALT, alanine transaminase; anti-HBc, anti-hepatitis B core; AST, aspartate transaminase; ETV, entecavir; HCV, hepatitis C virus; HSCT, hematopoietic stem cell transplantation; INR, international normalized ratio; Mono, monotherapy; S/CO, signal to cutoff ratio; TDF, tenofovir disoproxil fumarate; Tx, daratumumab treatment; WBC, white blood cell.

daratumumab cycles was 2.5 (1–18), and the median level of HBV DNA was 7.0 (4.6–8.2) log IU/mL (Table 1). Among these 6 patients, 2 (2.2%) had severe hepatitis. All the patients with reactivation were treated with potent antiviral drugs (TDF, n = 2; entecavir, n = 4) (Table 1). During the follow-up, 5 patients achieved maintained virological response with undetectable HBV DNA levels, one of whom achieved HBsAg seroclearance. One patient with HBV reactivation and severe hepatitis expired due to hepatic failure. The frequency of high HBsAb titer (>100 IU/L) was lower in patients with reactivation than without reactivation (16.7% vs 31.0%, respectively), although the difference was not statistically significant (Table 2).

The patient who expired due to hepatic failure was 69 years old and had suffered from MM (clonal bone marrow plasma cells >60%, stage IIIA) with t(11;14) for 6 years. Before daratumumab monotherapy, his disease was refractory to standard treatments. At the start of daratumumab, he had normal liver function with negative HBsAg. He had no history of alcohol consumption or other hepatotoxic drugs use. At the time of starting 3rd daratumuab cycle, treatment was stopped because of a sudden increase in alanine aminotransferase levels to 310 mg/dL (Supplementary Figure 2). At that time, his negative HBsAg result turned positive with HBV DNA level of 6.3 log IU/mL and a total bilirubin level of 7.06 mg/dL. Computed tomography images demonstrated mildly enlarged liver with periportal edema without evidence of underlying chronic liver diseases. Although TDF treatment was started soon, total bilirubin level constantly increased, and hepatic encephalopathy developed. After 15 days of TDF treatment, hepatorenal syndrome developed. Finally, he died due to hepatic failure after 17 days of TDF treatment (Supplementary Figure 2).

DISCUSSION

This is the first report to our knowledge showing the risk of reactivation of resolved HBV infection in HBsAg-negative patients after daratumumab therapy. Reactivation of resolved infection developed in 6 patients (6.5%), and one of them died due to hepatic failure. Recently, Kikuchi et al reported one case of HBV reactivation after daratumumab, but the patient had normal liver enzyme levels and no severe hepatitis [7]. According to our study, daratumumab treatment showed a considerable risk of reactivation of resolved HBV infection with the possibility of hepatic failure.

Although the pathogenesis of reactivation of resolved HBV infection is not clear, the CD38, a target of daratumumab, is expressed in not only myeloma cells but also expressed in nonmalignant plasma cells [8, 9]. Therefore, daratumumab may lead to the loss of humoral immunity against HBV and increase the risk of reactivation [10]. Indeed, rituximab, a chimeric anti-CD20 monoclonal antibody, demonstrated the importance of humoral immunity against reactivation of HBV [11].

A high risk (7–42%) of HBV reactivation in HBsAg-negative/anti-HBc-positive patients was reported in patients with rituximab treatment, and prophylactic antiviral treatment is strongly recommended in this group when rituximab is administered [5, 10]. In our study, the risk (6.5%) of reactivation of HBsAg (–) patients after daratumumab treatment is comparable to as those in rituximab. The risk for reactivation became even higher (12.5%), when only considering patients with HBsAg-negative/anti-HBc-positive serology (3 among 24 patients). In this study, the frequency of high HBsAb titer (>100 IU/L), one of the protective factors for reactivation in rituximab [12], was lower in patients with reactivation than without reactivation (16.7% vs 31.0%, respectively), although the difference was not statistically significant. Higher titer of protective antibody means stronger virus-specific adaptive immune responses, which may hamper viral reactivation after B cell- or plasma cell-depleting treatments.

Meanwhile, our institution previously reported that patients with reactivation of resolved HBV infection after rituximab or hematopoietic stem cell transplantation experience a high rate of HBsAg seroclearance (functional cure) following early antiviral treatment [6, 13]. This may also apply to the reactivation cases after daratumumab. In the present study, one patient with reactivation of resolved HBV infection experienced HBsAg seroclerance after antiviral therapy. To establish the optimal strategy for antiviral therapy, future studies with larger scales are needed to find out the typical timing and the risk period of the reactivation during and after daratumumab treatment.

Overall, this study shows a considerable risk of reactivation of resolved HBV infection after daratumumab treatment in MM patients. Therefore, checking the baseline HBsAg/Ab and anti-HBc and regular follow-up of liver function/HBV serological status are required in patients receiving daratumumab.

Table 2. Comparison of Hepatitis B Virus (HBV) Serological Markers Between the Patients With and Without Reactivation

	Patients With Reactivation (n = 6)	Patients Without Reactivation (n = 87)
HBsAb titer (IU/L) (median, range)	59.4 (3.8–98.7)	12.5 (2.0–130.4)
HBsAb positivity (>10 IU/L) (n, %)	4 (66.7%)	45 (51.7%)
High HBsAb titer (>100 IU/L) (n, %)	1 (16.7%)	27 (31.0%)
Patients with anti-HBc results (n)	4	57
Anti-HBc titer (S/CO) (median, range)	0.24 (0.1–3.06)	0.85 (0.02–7.43)

Abbreviations: anti-HBc, anti-hepatitis B core; S/CO, signal to cutoff ratio.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Supplementary Figure 1. Patient cohort. MM, multiple myeloma; anti-HBc, anti-hepatitis B core.
Supplementary Figure 2. Timeline of the patient who expired due to hepatic failure caused by HBV reactivation after daratumumab treatment.

Notes

Author contributions.

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