A Prospective Study of Preemptive Tenofovir Disoproxil Fumarate Therapy in HBsAg-Positive Patients With Diffuse Large B-Cell Lymphoma Receiving Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone

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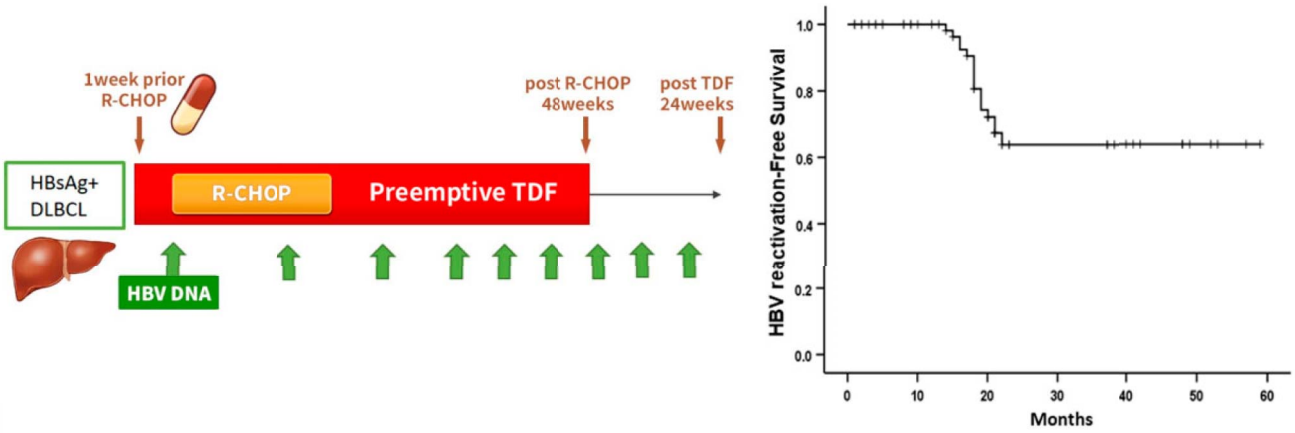
Tenofovir for HBsAg positive patients with diffuse large B-cell lymphoma receiving R-CHOP: observational study



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LIVER

INTRODUCTION: **This prospective study aimed to investigate the efficacy and safety of preemptive antiviral therapy with tenofovir disoproxil fumarate (TDF) for HBsAg-positive patients with newly diagnosed diffuse large B-cell lymphoma receiving rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemotherapy.**

METHODS: **We enrolled 73 patients from 20 institutions. The primary end point was the absolute risk of hepatitis B virus (HBV)-related hepatitis during preemptive TDF therapy and for 24 weeks after withdrawal from TDF. Hepatitis was defined as a more than 3-fold increase in serum alanine aminotransferase from baseline or an alanine aminotransferase level of ≥100 U/L. HBV-related hepatitis was defined as hepatitis with an increase in serum HBV-DNA to >10 times that of the pre-exacerbation baseline or an absolute increase of ≥20,000 IU/mL compared with the baseline.**

RESULTS: **No patient developed HBV reactivation or HBV-related hepatitis during preemptive antiviral therapy (until 48 weeks after completion of R-CHOP chemotherapy) with TDF. All adverse events were grade 1 or 2. HBV reactivation was reported in 17 (23.3%) patients. All HBV reactivation was developed at a median of 90 days after withdrawal from TDF (range, 37–214 days). Six (8.2%) patients developed HBV-related hepatitis at a median of 88 days after withdrawal from TDF (range, 37–183 days).**

DISCUSSION: **Preemptive TDF therapy in HBsAg-positive patients with diffuse large B-cell lymphoma receiving R-CHOP chemotherapy was safe and effective for preventing HBV-related hepatitis. However, a long-term maintenance strategy of preemptive TDF therapy should be recommended because of the relatively high rate of HBV-related hepatitis after withdrawal from TDF (ClinicalTrials.gov ID: NCT02354846).**

KEYWORDS: diffuse large B-cell lymphoma; hepatitis B virus; antiviral therapy; tenofovir disoproxil fumarate

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/C865

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INTRODUCTION

A relatively high incidence of malignant lymphoma has been reported in patients with positive hepatitis B surface antigen (HBsAg). In particular, the incidence of diffuse large B-cell lymphoma (DLBCL) in HBsAg-positive patients is 6.86 per 100,000 person-years, approximately twice that of the general population (1). The reactivation of the hepatitis B virus (HBV) in HBsAg-positive patients with malignant lymphoma is associated with immunosuppression caused by intensive chemotherapy for treating underlying malignant lymphoma. Steroid-containing chemotherapies such as cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), anti-CD20 monoclonal antibodies such as rituximab, and hematopoietic stem cell transplantation are well-known risk factors for HBV reactivation (2–4). Rituximab plus CHOP (R-CHOP) is the current standard regimen for newly diagnosed DLBCL, as it has significantly improved treatment outcomes in patients with DLBCL (5). However, rituximab-containing regimens in HBsAg-positive patients can increase the risk of HBV reactivation during intensive chemotherapy and can lead to delays or premature termination of chemotherapy (6,7). Moreover, immune recovery following the administration of rituximab is delayed for nearly a year, conferring a risk of HBV reactivation after the completion of chemotherapy. Therefore, the prevention of HBV reactivation during chemotherapy is vital in HBsAg-positive patients with DLBCL.

Preemptive therapy with lamivudine can effectively prevent HBV reactivation in HBsAg-positive patients with lymphoma undergoing conventional chemotherapy (8–10). Nevertheless, HBV reactivation occurs in 10%–30% of HBsAg-positive patients receiving rituximab-containing chemotherapy regimens despite using lamivudine prophylaxis (6,7,11). Therefore, more potent antiviral agents such as entecavir or tenofovir disoproxil fumarate (TDF) are usually recommended for high-risk patients receiving rituximab-containing chemotherapy. In a previous study, prophylactic use of entecavir significantly reduced the risk of HBV reactivation (7,11–13) and improved survival (14) in HBsAg-positive patients treated with rituximab-containing chemotherapy. TDF is the only nucleotide analog that does not have resistance and is a drug for patients resistant to previous treatments (15). However, the efficacy and safety of preemptive antiviral therapy with TDF to prevent HBV reactivation caused by immunosuppression have not been elucidated. Specifically, to our knowledge, no prospective trial has evaluated the efficacy or safety of preemptive therapy with TDF in HBsAg-positive patients with DLBCL receiving rituximab-containing chemotherapy. Furthermore, the optimal duration of prophylactic antiviral therapy for HBsAg-positive patients with DLBCL receiving rituximab-containing chemotherapy has not been determined. The European Association for the Study of the Liver and National Comprehensive Cancer Network recommend antiviral therapy during chemotherapy and maintaining prophylaxis up to 12 months after the completion of treatment (13,16). In this study, we investigated the absolute risk of HBV reactivation during preemptive therapy with TDF (from 1 week before R-CHOP chemotherapy up to 48 weeks after the completion of R-CHOP

chemotherapy) and monitored HBV reactivation for at least 24 weeks after the withdrawal of TDF prophylaxis in HBsAg-positive patients treated with R-CHOP chemotherapy.

METHODS

Study design

This study was a prospective, multicenter, observational study conducted in December 2015 in Korea among 20 institutions. Written informed consent was obtained from all patients with untreated DLBCL in accordance with the Declaration of Helsinki. This trial was approved by the institutional review boards and ethics committees of each participating institution. The trial is registered on the National Cancer Institute website (trial number NCT02354846).

Patient eligibility

Eligible patients were aged >18 years with histologically confirmed newly diagnosed CD20-positive DLBCL according to the World Health Organization classification, regardless of the stage, without prior chemotherapy or radiotherapy for DLBCL. The inclusion criteria included seropositive for HBsAg, Eastern Cooperative Oncology Group (ECOG) performance status ≤2, adequate hematologic laboratory results (hemoglobin ≥ 9 g/dL, absolute neutrophil count ≥ 1,500/μL, platelet count ≥ 75,000/μL, and other abnormalities caused by bone marrow involvement due to lymphoma), and adequate heart function (cardiac left ventricular ejection fraction ≥ 50% and no clinically significant abnormal findings), renal function (serum creatinine level <2 mg/dL or 177 μmol/L), and liver function (assessed by levels of alanine aminotransferase [ALT] and aspartate aminotransferase [AST] < 2 × the upper limit of the normal range [ULN]). Exclusion criteria consisted of other subtypes of lymphoma except DLBCL, primary central nervous system lymphoma, lactation or pregnancy, a life expectancy of fewer than 6 months, unsuitable for R-CHOP chemotherapy, a history of human immunodeficiency virus and hepatitis C virus infection, previous treatment with antiviral therapy known to have activity against HBV (e.g., alpha-interferon, lamivudine, telbivudine, clevudine, adefovir, entecavir, or TDF) within the previous 6 months, and any evidence of hepatocellular carcinoma or decompensated liver disease.

Treatment regimen

The R-CHOP-21 regimen, comprising rituximab (375 mg/m^2; intravenous), cyclophosphamide (750 mg/m^2; intravenous), doxorubicin (50 mg/m^2; intravenous), and vincristine (1.4 mg/m^2, maximum 2.0 mg; intravenous) on day 1 and prednisone (100 mg/d; oral) on days 1–5, was administered every 3 weeks. Additional consolidative radiotherapy or autologous hematopoietic stem cell transplantation was allowed after the completion of the planned cycles of R-CHOP chemotherapy, according to the discretion of each participating institution.

Prophylactic TDF at a dose of 300 mg/d was orally initiated 1 week before chemotherapy and withdrawn 48 weeks after completion of R-CHOP chemotherapy. TDF was used every 48 hours in patients with an estimated glomerular filtration rate of 30–49 mL/min/1.73 m^2 and every 72–96 hours in patients with a glomerular filtration rate of 10–29 mL/min/1.73 m^2. Complete blood cell counts and liver and renal function were monitored before each chemotherapy cycle and then every 3 months after the completion of chemotherapy. Routine monitoring was continued every 12 weeks for 24 weeks after the withdrawal of antiviral prophylaxis. The HBV-DNA level, which was measured by real-time viral polymerase chain reaction assays, was monitored before the first chemotherapy cycle, midcycle (third or fourth cycle of chemotherapy), every 12 weeks for 48 weeks after the completion of chemotherapy, and every 12 weeks for the first 24 weeks after withdrawal of antiviral prophylaxis. Thereafter, monitoring was continued according to the policy of each participating institution. All patients underwent response evaluation in accordance with the international workshop criteria. Safety profiles were evaluated by the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

Definitions and end points

The primary efficacy end point for this study was the percentage and number of patients with hepatitis due to HBV reactivation (HBV-related hepatitis) during the preemptive TDF therapy and for 24 weeks after withdrawal from TDF. At baseline, a diagnosis of cirrhosis was made by the following clinical criteria as follows: (i) history of overt complication of cirrhosis such as ascites, variceal hemorrhage, and hepatic encephalopathy; (ii) platelet count < 100,000/μL and imaging (ultrasound or computed tomography) findings suggestive of cirrhosis such as blunted or nodular liver edge accompanied by splenomegaly (>12 cm); or (iii) presence of esophageal or gastric varices accompanied by chronic liver disease in the imaging study (17). We excluded the patients with decompensated cirrhosis in this study.

Hepatitis was defined as a more than 3-fold increase in the serum ALT level or an absolute increase in the level of ALT of >100 U/L compared with the baseline level on 2 consecutive determinations at least 5 days apart at a predefined interval of laboratory assessment; a repeat ALT test was completed within 4 weeks to confirm the presence of hepatitis. Hepatitis severity was defined according to the Common Terminology Criteria for Adverse Events version 4.0 as follows: grade 1, ALT elevation up to 3.0 × the ULN; grade 2, ALT of 3.0–5.0 × the ULN; grade 3, ALT of 5.0–20.0 × the ULN; and grade 4, ALT > 20.0 × the ULN. HBV reactivation was defined as an increase in serum HBV-DNA to more than 10 × that of the pre-exacerbation baseline or an absolute increase to 20,000 IU/mL or greater compared with the baseline value and the shift from serum HBV-DNA negativity to positivity. HBV-related hepatitis was defined as HBV reactivation accompanied by hepatitis. Chemotherapy disruption due to hepatitis was defined as either premature termination or delay of more than 8 days between chemotherapy cycles. Delayed HBV-related hepatitis was defined as hepatitis related to HBV reactivation occurring more than 6 months after the initiation of chemotherapy. Mortality caused by hepatic failure was also documented.

Statistical analysis

Numerical data were expressed as descriptive statistics. The Pearson χ^2 or Fisher exact test was used to investigate the relationships between categorical variables. Univariable analysis was performed using a logistic regression model to assess the factors associated with HBV reactivation and HBV-related hepatitis. Time to hepatitis was defined as the time from the diagnosis of DLBCL to the first development of hepatitis. Reactivation-free survival was defined as the interval between the date of TDF administration to the date of HBV reactivation or the date of final follow-up. Progression-free survival (PFS) was defined as the time from treatment initiation to the first recording of relapse, disease

Table 1. Baseline characteristics of HBsAg-positive patients with diffuse large B-cell lymphoma

Characteristics	No. of (percentage) patients
Age, median (range, yr)	56 (29–89)
Sex	
Male/female	41 (56.2%)/32 (43.8%)
Ann Arbor stage	
Stage I/II	21 (28.8%)
Stage III/IV	52 (71.2%)
ECOG performance status	
0–1/2	65 (89.0%)/8 (11.0%)
Liver involvement	3 (4.1%)
Bone marrow involvement	9 (12.3%)
International Prognostic Index	
0–1	28 (38.4%)
2/3	17 (23.3%)/22 (30.1%)
4–5	6 (8.2%)
Normal AST/ALT	56 (76.7%)/65 (89.0%)
Liver cirrhosis (compensated)	7 (9.6%)
Positive hepatitis B core antibody (anti-HBc) status[a]	63 (86.3%)
Positive hepatitis B e antigen (HBeAg) status[b]	17 (23.3%)
Baseline HBV-DNA, median (range, IU/mL)	924 (0–7.16 × 10^8)
Undetectable	14 (19.2%)
>20,000 IU/mL	15 (20.5%)
Cycles of R-CHOP, median (range)	6 (1–8)
6 cycles of R-CHOP	51 (69.8%)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ECOG, Eastern Cooperative Oncology Group; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.
[a]The data are missing for 1 patient.
[b]The data are missing for 3 patients.

progression, or death from any cause. Overall survival (OS) was defined as the time from initial treatment to death from any cause or the date of the final follow-up evaluation. Statistical analysis was performed using SPSS 23.0 (IBM, Armonk, NY).

RESULTS

Patient characteristics

Between December 2015 and November 2018, 73 HBsAg-positive patients with newly diagnosed DLBCL were enrolled in this study, including 41 (56.2%) men and 32 (43.8%) women. A total of 52 (71.2%) patients had stage III/IV disease, and 8 (11.0%) had a poor ECOG performance status (score: 2). A baseline serum HBV-DNA titer of ≤ 20,000 IU/mL was observed in most patients (79.5%). A total of 66 patients with noncirrhosis and 7 patients with cirrhosis were included in this study. Three patients had no data for hepatitis B e antigen (HBeAg) (2 patients with noncirrhosis and 1 patient with cirrhosis). Forty-eight patients were HBeAg negative with noncirrhosis, among whom 16 had an HBV-DNA level of >2,000 IU/mL, with an AST/ALT level of <2 × the ULN. Among the 16 HBeAg-positive patients with noncirrhosis, an HBV-DNA level of >20,000 IU/mL was detected in 13 patients. However, none of these patients had an AST/ALT level of >2 × the ULN. In addition, 7 patients had compensated liver cirrhosis, and 3 patients had an HBV-DNA level of >2,000 IU/mL, all of whom had normal AST/ALT levels. The patient characteristics are summarized in Table 1.

Treatment outcomes

The patients received a median of 6 cycles (range, 3–8 cycles) of R-CHOP chemotherapy in this study. The median follow-up duration for all patients was 21 months. The median PFS and OS were not reached. The 2-year OS was 91.8%, and the 2-year PFS was 76.5%. The 2-year HBV reactivation-free survival was 63.8% (Figure 1a), and the HBV-related hepatitis-free survival was 86.4% (Figure 1b). Forty-eight patients completed the planned prophylactic antiviral therapy (preemptive therapy with TDF from 1 week before R-CHOP chemotherapy up to 48 weeks after the completion of R-CHOP chemotherapy), and 25 patients stopped the antiviral treatment early due to relapse of underlying DLBCL (n = 12), withdrawal of informed consent (n = 7), chemotherapy-related mortality (n = 1), transfer to another hospital or loss of follow-up (n = 3), or other reasons (n = 2). Among the 48 patients who completed the planned prophylactic antiviral therapy, HBV-DNA was not detected immediately before the planned discontinuation of TDF. The median duration of TDF treatment was 15.0 months (range, 0.8–20.1 months). Among the 73 patients, 13 (17.8%) developed hepatitis, and 17 (23.3%) experienced HBV reactivation (Table 2), whereas HBV-related hepatitis was observed in 6 (8.2%) patients after withdrawal from TDF prophylaxis (Table 2). None of the patients were diagnosed with HBV-related hepatitis during TDF prophylaxis. All 6 patients with HBV-related hepatitis developed after the withdrawal from TDF prophylaxis (Table 2). None of the patients experienced premature termination of chemotherapy or a delay of chemotherapy due to underlying HBV-related problems, HBV-related liver decompensation, or HBV-related mortality in this study.

HBV reactivation

Among the total study population, HBV reactivation was reported in 17 (23.3%) patients (Table 3). The median time to occurrence of HBV reactivation after the completion of R-CHOP chemotherapy was 444 days (range, 280–549 days). HBV reactivation was developed at a median of 90 days after withdrawal from TDF (range, 37–214 days). In addition, no patients developed HBV reactivation during preemptive antiviral therapy with TDF. At the time of HBV reactivation, the median serum level of HBV-DNA was 118,600 IU/mL (range, 151–47,200,000 IU/mL). Among the 17 cases of HBV reactivation, 6 were classified as HBV-related hepatitis. TDF was reused in 11 patients with HBV reactivation, and the outcome was successful.

Hepatitis due to HBV reactivation (HBV-related hepatitis)

There was no patient who developed HBV-related hepatitis during preemptive antiviral therapy with TDF. Among the 6 patients who developed HBV-related hepatitis (Table 4), the median time to occurrence after the completion of R-CHOP chemotherapy was 445 days (range, 280–549 days), and these 6 patients were classified as the delayed HBV-related hepatitis defined as hepatitis related to

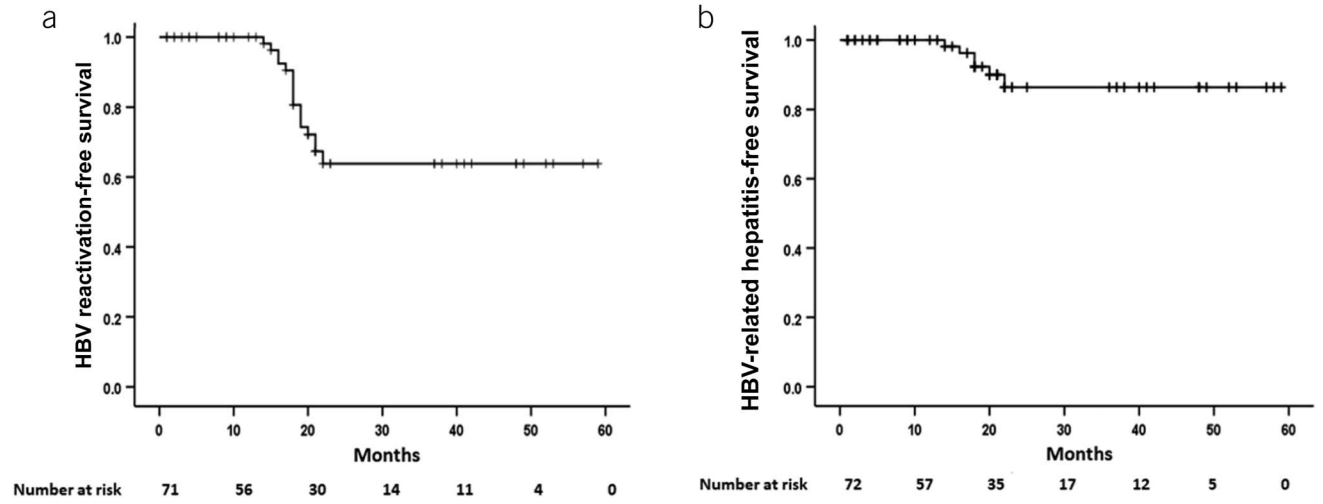

Figure 1. Kaplan-Meier analyses of (**a**) HBV reactivation-free survival and (**b**) HBV-related hepatitis-free survival of 73 hepatitis B virus–positive patients with diffuse large B-cell lymphoma receiving R-CHOP chemotherapy.

HBV reactivation occurring more than 6 months after the initiation of chemotherapy. Moreover, the overall HBV-related hepatitis occurred at a median of 88 days after withdrawal from TDF (range, 37–214 days). One patient who developed HBV-related hepatitis 280 days after the completion of R-CHOP chemotherapy stopped the preemptive antiviral therapy with TDF 196 days after the completion of R-CHOP chemotherapy due to the early withdrawal of his informed consent. The remaining 5 cases of HBV-related hepatitis occurred after the planned maintenance of antiviral therapy with TDF for 48 weeks after the completion of R-CHOP chemotherapy. At the time of HBV-related hepatitis, the median serum level of HBV-DNA was 133,000 IU/mL (range, 9,000–47,200,000 IU/mL). Antiviral therapy for HBV-related hepatitis was initiated with TDF for all 6 patients, and the outcomes were successful.

Table 2. Clinical characteristics of hepatitis, HBV reactivation, and HBV-related hepatitis in HBsAg-positive patients with diffuse large B-cell lymphoma

Characteristics	No. of (percentage) patients
Absolute risk of hepatitis	13 (17.8%)
Severity of hepatitis	
Grade 1	2
Grade 2	4
Grade 3	4
Grade 4	3
Chemotherapy disruption	
Premature termination	0
Chemotherapy delay: > 8 d between chemotherapy cycles	0
HBV reactivation	17 (23.3%)
HBV reactivation during tenofovir prophylaxis	0
HBV reactivation after the withdrawal from tenofovir prophylaxis	17
HBV-related hepatitis	6 (8.2%)
HBV-related hepatitis during tenofovir prophylaxis	0
HBV-related hepatitis after the withdrawal from tenofovir prophylaxis	6

HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

Factors associated with HBV reactivation and HBV-related hepatitis

The median age was significantly lower in patients with HBV reactivation (49.7 vs 58.6, $P = 0.004$). According to the univariable analysis for detecting factors associated with HBV reactivation, only age $\leq$ 60 years was the associated risk factor for increasing HBV reactivation (34.8% vs 3.8%; $P = 0.015$). For HBV-related hepatitis, the univariable analysis revealed that only the high-intermediate or high International Prognostic Index was associated with a higher risk for HBV-related hepatitis (17.9% vs 2.2%, $P = .045$). Other factors such as sex, poor ECOG performance status, liver involvement, bone marrow involvement, advanced Ann Arbor stage, hepatitis B e antigen positivity, and the number of cycles of R-CHOP chemotherapy were not considered risk factors associated with HBV reactivation or HBV-related hepatitis (see Supplementary Table 1, http://links.lww.com/AJG/C865).

Safety

All observed adverse events were grade 1 or 2. Grade 3 or 4 adverse events related to TDF were not observed in this study. Four (5.4%) patients with grade 1 nausea, 2 (2.7%) patients with grade 1 heartburn, 1 patient with grade 1 diarrhea, 1 patient with grade 1 vomiting, and 1 patient with grade 2 abdominal pain were reported (see Supplementary Table 2, http://links.lww.com/AJG/C865).

DISCUSSION

This is the first prospective, multicenter, observational study of preemptive TDF therapy (300 mg/d) in HBsAg-positive patients with newly diagnosed DLBCL who were treated with R-CHOP chemotherapy. Our study showed that TDF from 1 week before R-CHOP chemotherapy up to 48 weeks after the completion

Table 3. Clinical data and outcomes of 17 patients with HBV reactivation

					HBV reactivation							
Patient no.	Age, yrs	Sex	Ann Arbor stage	IPI	No. of d after the last cycle of R-CHOP	No. of d after the last dose of tenofovir prophylaxis	Peak HBV-DNA (IU/mL)	HBeAg	Baseline ALT (IU/L)	Peak ALT(IU/L)	Management for HBV reactivation	Outcome
1	41	M	4	3	280	84	9,000	Negative	31	141	Tenofovir	Alive and well
2	66	F	4	4	444	98	2,556,238	Positive	36	90	Tenofovir	Alive and well
3	43	F	4	3	441	84	256	Negative	35	46	Observation	Alive and well
4	56	M	2	0	462	99	918	Negative	13	15	Observation	Alive and well
5	35	M	1	0	346	214	34,000,000	Negative	38	49	Observation	Alive and well
6	53	M	3	2	425	90	118,000	Negative	22	19	Tenofovir	Alive and well
7	44	M	3	3	433	92	47,200,000	Positive	33	1,653	Tenofovir	Alive and well
8	49	F	1	1	412	74	151	Negative	15	11	Observation	Alive and well
9	39	M	4	3	534	148	770,000	Positive	7	15	Observation	Alive and well
10	45	M	3	1	466	74	27,600,000	Negative	19	29	Observation	Alive and well
11	56	F	1	0	475	90	70,000	Negative	23	88	Tenofovir	Alive and well
12	60	M	4	3	476	102	68,000	Negative	20	655	Tenofovir	Alive and well
13	56	M	4	3	457	77	198,000	Negative	27	273	Tenofovir	Alive and well
14	36	M	4	1	453	74	88,000	Negative	18	45	Tenofovir	Alive and well
15	58	M	4	1	420	85	5,187,369	Positive	51	22	Tenofovir	Alive and well
16	55	F	4	3	319	37	50,800	Negative	16	2,176	Tenofovir	Alive and well
17	52	M	4	2	549	183	1,362,725	Negative	38	1,444	Tenofovir	Alive and well

ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; IPI, International Prognostic Index; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

effectively and safely prevented HBV reactivation and HBV-related hepatitis in this population.

Currently, limited data are available regarding TDF prophylaxis, although international guidelines, including those of the European Association for the Study of the Liver and National Comprehensive Cancer Network, recommend entecavir or TDF prophylaxis for HBsAg-positive patients with DLBCL. Therefore, our study confirms the validity of these recommendations. In a previous study in Italy, 39 HBsAg-positive patients with DLBCL were prospectively recruited, treated with TDF, and compared with a historical control (38 patients treated with lamivudine). However, that study only included advanced-stage DLBCL (Ann Arbor stages III or IV) (18). Notably, we found that HBV reactivation and HBV-related hepatitis usually occurred late after withdrawal from TDF prophylaxis (median of 90 days and 88 days after withdrawal from TDF, respectively).

According to the results of a prospective randomized trial of entecavir vs lamivudine for the prevention of HBV reactivation (12), preemptive entecavir therapy is preferable in HBsAg-positive patients with DLBCL receiving R-CHOP chemotherapy. However, the duration of antiviral prophylaxis with entecavir was only 6 months after the completion of R-CHOP chemotherapy, and no

Table 4. Clinical data and outcomes of 6 patients with HBV-related hepatitis

							HBV-related hepatitis						
Patient no.	Age, yr	Sex	Ann Arbor stage	IPI	HBeAg status at baseline	No. of cycles of R-CHOP before hepatitis	No. of days after the last cycle of R-CHOP	No. of d after the last dose of tenofovir prophylaxis	Peak HBV-DNA (IU/mL)	Baseline ALT (IU/L)	Peak ALT(IU/L)	Antiviral treatment for HBV-related hepatitis	Outcome
1	41	M	4	3	Negative	8	280	84	9,094	31	141	Tenofovir	Alive and well
7	44	M	3	3	Negative	6	433	92	47,200,000	33	1,653	Tenofovir	Alive and well
12	60	M	4	3	Positive	6	476	102	68,000	20	655	Tenofovir	Alive and well
13	56	M	4	3	Negative	6	457	77	198,000	27	273	Tenofovir	Alive and well
16	55	F	4	3	Negative	6	319	37	50,800	16	2,176	Tenofovir	Alive and well
17	52	M	4	2	Negative	6	549	183	1,362,725	38	1,444	Tenofovir	Alive and well

ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; IPI, International Prognostic Index; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

reported case of HBV reactivation occurred after withdrawal from entecavir treatment. This trial did not evaluate late HBV reactivation and HBV-related hepatitis after withdrawal from entecavir prophylaxis (12). Nevertheless, most guidelines recommend to commence preemptive antiviral therapy before starting chemotherapy and to continue the prophylaxis for 12 months after the completion of chemotherapy without solid evidence (13,16). Therefore, it is a clinically very important process to reevaluate the appropriate duration of preemptive antiviral therapy (at least 1 year of antiviral therapy after the completion of chemotherapy) and emphasize the monitoring of patients for a sufficient duration to detect the late occurrence of HBV reactivation and HBV-related hepatitis after the withdrawal of preemptive antiviral therapy.

In the present study, we confirmed the role of 1 year of preemptive TDF therapy after the completion of chemotherapy in HBsAg-positive patients with DLBCL receiving R-CHOP chemotherapy because no patient exhibited HBV reactivation or HBV-related hepatitis during 1 year of preemptive TDF therapy. In contrast, in the previous study comparing entecavir and lamivudine, 4 (6.6%) of 61 patients developed HBV reactivation during 6-month entecavir prophylaxis (12). The high antiviral potency and higher genetic barrier of TDF compared with those of entecavir combined with a longer duration of preemptive TDF therapy could have resulted in the lack of HBV reactivation and HBV-related hepatitis in this study (19). In addition, we observed late development of HBV reactivation and HBV-related hepatitis after the withdrawal of TDF prophylaxis (23.3% of HBV reactivation and 8.2% of HBV-related hepatitis). Because all 6 patients who developed late HBV-related hepatitis after withdrawal from TDF prophylaxis were successfully treated with readministration of TDF, the importance of long-term regular monitoring including serum HBV-DNA tests should be emphasized for patients who stop antiviral prophylaxis. We observed a higher rate of HBV reactivation in patients aged ≤60 years compared with those aged >60 years after the withdrawal of TDF prophylaxis (34.8% vs 3.8%, $P = 0.015$). Although the mechanism by which age affects HBV reactivation is unknown, this result suggests that more attention is necessary for patients younger than 60 years after completion of chemotherapy and preemptive antiviral therapy. Moreover, the optimal duration of antiviral prophylaxis for preventing HBV reactivation or HBV-related hepatitis in high-risk patients should be further investigated in future studies.

This study had a few limitations. Because this trial was an observational study, we could not define the most effective duration of preemptive antiviral therapy. However, approximately 1 year of maintaining preemptive TDF therapy after the completion of R-CHOP chemotherapy was insufficient for preventing late HBV reactivation and HBV-related hepatitis because we observed a relatively high incidence of late HBV reactivation and HBV-related hepatitis after withdrawal from approximately 1 year of TDF prophylaxis. Therefore, the current recommended duration of 1 year of preemptive antiviral prophylaxis after the completion of chemotherapy requires modification. Because several HBV reactivation and HBV-related hepatitis events were observed at a median of about 90 days after the completion of the planned 48 weeks of TDF prophylaxis, we recommend close monitoring for HBV reactivation in HBsAg-positive patients with DLBCL who receive R-CHOP chemotherapy for at least 3–6 months even after the withdrawal of antiviral prophylaxis. In addition, we have to find a high-risk group of HBV reactivation with only 1 year of antiviral prophylaxis after the completion of rituximab-based chemotherapy in a future study with a larger population. Regarding patients with cirrhosis, although our study design ceased prophylactic TDF after the planned 48 weeks of administration, HBV reactivation and hepatitis flares in this population could result in irreversible liver damage after the withdrawal of antiviral prophylaxis. Because the most recent American Association for the Study of Liver Diseases guidelines recommend antiviral therapy even for patients with cirrhosis with low-level viremia (<2,000 IU/mL) to prevent decompensation (20), different prophylactic strategies should be

applied for the patients with liver cirrhosis, and the duration of prophylactic antiviral therapy in patients with cirrhosis might be indefinite. Tenofovir alafenamide (TAF) is a new tenofovir prodrug showing noninferior efficacy for treating HBeAg-positive/-negative chronic HBV infection and a better safety profile than that of TDF in phase 3 trials (21,22). As TAF is recommended as the first-line antiviral therapy for patients with chronic hepatitis B along with entecavir and TDF, the efficacy and safety of TAF as preemptive antiviral therapy in HBsAg-positive patients with DLBCL undergoing R-CHOP chemotherapy should be evaluated in the near future.

Preemptive TDF therapy in HBsAg-positive patients with DLBCL receiving R-CHOP chemotherapy was safe and effective for preventing HBV-related hepatitis. To the best of our knowledge, this is the first prospective trial to determine the role of preemptive TDF prophylaxis in patients with DLBCL receiving R-CHOP chemotherapy. Therefore, TDF should be recommended for HBsAg-positive patients with DLBCL during chemotherapy and thereafter. However, a long-term maintenance strategy of preemptive TDF therapy might be recommended because of the relatively high rate of HBV-related hepatitis after withdrawal of TDF.

CONFLICTS OF INTEREST

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Study Highlights

WHAT IS KNOWN

- ✓ Antiviral therapy with entecavir prevents hepatitis B virus (HBV) reactivation and hepatitis in patients who undergo rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemotherapy.

WHAT IS NEW HERE

- ✓ No patient developed HBV reactivation or HBV-related hepatitis during preemptive antiviral therapy (until 48 weeks after completion of R-CHOP chemotherapy) with tenofovir disoproxil fumarate (TDF) in hepatitis B surface antigen–positive patients with diffuse large B-cell lymphoma receiving R-CHOP chemotherapy.
- ✓ The absolute risk of HBV reactivation in hepatitis B surface antigen–positive patients with diffuse large B-cell lymphoma who received R-CHOP chemotherapy and preemptive antiviral therapy with TDF was 23.3%, and all HBV reactivation developed after withdrawal from TDF (median 90 days).
- ✓ 8.2% of patients developed HBV-related hepatitis at 88 days (median) after withdrawal from TDF.

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