TO THE EDITOR:

Tenofovir vs lamivudine for the prevention of hepatitis B virus reactivation in advanced-stage DLBCL

Marco Picardi,[1] Roberta Della Pepa,[2] Claudia Giordano,[2] Irene Zacheo,[2] Novella Pugliese,[2] Chiara Mortaruolo,[2] Fabio Trastulli,[2] Antonio Giordano,[2] Mariano Lucignano,[2] Maria Di Perna,[2] Marta Raimondo,[2] Claudia Salvatore,[3] and Fabrizio Pane[2]

[1]Department of Advanced Biomedical Sciences and [2]Department of Clinical Medicine and Surgery, Federico II University Medical, School, Naples, Italy; and [3]Department of Economics, University of Molise, Campobasso, Italy

The anti-CD20 monoclonal antibody rituximab, together with anthracycline, in hepatitis B surface antigen (HBsAg) healthy carriers affected by non-Hodgkin lymphoma (NHL) increases hepatitis B virus (HBV) reactivation risk.[1] Oral primary antiviral prophylaxis (PAVP) is a common strategy in this setting.[2-4] Lamivudine (LAM) has shown to be effective.[5] HBsAg-seropositive patients undergoing R-CHOP-21 (IV cyclophosphamide [750 mg/m^2], doxorubicin [50 mg/m^2], vincristine [1-4 mg/m^2, maximum dose 2 mg], and rituximab [375 mg/m^2] on day 1, and oral prednisolone [100 mg] on days 1-5, administered every 21 days for a total of 6 cycles)[6,7] for diffuse large B-cell NHL (DLBCL)[8] with an adverse International Prognostic Index (IPI) score[9] are at high risk for antiviral prophylaxis failure.[2-5] Tenofovir disoproxil fumarate (TDF) is a new-generation oral nucleotide analog with stronger antiviral activity and a higher genetic barrier to resistance than LAM.[2-5] We report a prospective series of HBsAg-seropositive patients receiving TDF prophylaxis against HBV reactivation concurrently with R-CHOP-21 chemotherapy as remission induction for advanced-stage DLBCL.[6,7] We then compared TDF efficacy and safety rates in these patients with those of a historical cohort treated with LAM.

This study was conducted in the Hematology Unit of the Federico II University. All necessary approvals were obtained from our ethics committee. From February 2009 to June 2015, consecutive HBsAg-seropositive patients with newly diagnosed DLBCL scheduled to receive 6 cycles of R-CHOP-21 for adverse prognostic factors[9] received TDF (245 mg orally daily),[3,4] whereas LAM (100 mg orally daily) was administered to a cohort of patients with the same clinical characteristics from July 2004 to January 2009. The antiviral drug was begun 1 week before chemotherapy and was scheduled to continue for 12 months after the completion of chemotherapy.[10,11] Liver function biochemical tests and serum HBV DNA were monitored at baseline and then every 1 to 3 months.[10,11] At the indicated time points, patients also underwent assessment of estimated glomerular filtration rate (eGFR) and bone mineral density.[3,4] Efficacy analysis focused primarily on HBV reactivation (HBV DNA ≥ 2-log increase from baseline levels or new appearance of HBV DNA ≥ 100 IU/mL) and secondarily on acute hepatitis (≥3-fold increase in serum alanine aminotransferase level that exceeded the reference range) and chemotherapy disruption for HBV reactivation (premature termination of chemotherapy or a delay ≥7 days between chemotherapy cycles).[3,4] Safety analysis focused on kidney and bone toxicity.

During the 6-year prospective study period, 39 patients received TDF (TDF group). In the historical cohort, 38 patients received LAM (LAM cohort). These 77 patients, who constituted the entire population included in the final assessment (Table 1), were inactive HBsAg carriers with undetectable or low (n = 26; median 320 IU/mL) serum HBV DNA levels at baseline. Thirty-two patients in the LAM cohort and 39 patients in the TDF group received 6 cycles of R-CHOP-21, according to the standard schedule. The median duration of PAVP treatment was 18 months with LAM (range, 4-18) and with TDF (range, 12-18). Both antiviral prophylactic drugs were well tolerated with no discontinuations as a result of adverse events, toxicity, or noncompliance. Other supportive care measures (eg, pegfilgrastim, antimicrobials) were given equally to the patients in both groups. The median follow-up was 85.5 months in the LAM cohort vs 78 months in the TDF group. Emergent HBV DNA or exacerbation of HBV replication did not develop in any of the 39 patients in the TDF group compared with 15 of 38 patients in the LAM cohort (median serum HBV DNA level, 3.5×10^6 IU/mL; range, 1.4-7.0 $\times 10^6$; absolute risk reduction, 0.395; 95% confidence interval [CI], 0.229-0.553; $P < .0001$). Six reactivations appeared in patients with detectable serum HBV DNA (median, 200 IU/mL; range, 100-948) at pretreatment. The median time to HBV reactivation after immune-chemotherapy initiation was 6 months (range, 4-36), with 4 reactivations beyond 12 months. None of the patients in the TDF group developed acute hepatitis compared with 4 patients (with massive HBV replication) in the LAM cohort. Thus, the rate of HBV-related acute hepatitis was lower for the TDF group vs the LAM cohort (absolute risk reduction, 0.105; 95% CI, −0.005 to 0.241; $P = .054$). No patient in the TDF group and 6 patients in the LAM cohort experienced chemotherapy disruption for early HBV reactivation and/or HBV-related hepatitis (absolute risk reduction, 0.158, 95% CI, 0.035-0.304; $P = .012$). In the LAM cohort, the mean baseline eGFR was 95.3 ± 19.0 mL/min per 1.73 m^2, and this was 88.6 ± 21.0 mL/min per 1.73 m^2 (a reduction of 7%) at the end of the study. In the TDF group, the mean baseline eGFR was 94.3 ± 18.0 mL/min per 1.74 m^2 and 87.6 ± 20.0 mL/min per 1.74 m^2 at the end of the study (a reduction of 7.2%). Dual energy x-ray absorptiometry scanning from baseline to the end of the study revealed osteopenia in ~10% of the patients in each group. Three-year progression-free survival was 75.4% in the LAM cohort and 76.3% in the TDF group, and 3-year overall survival was 63.8% and 65.7%, respectively.

The Bay of Naples is considered endemic for chronic HBV infection[10,11]; thus, it is not uncommon that a candidate to antineoplastic treatment of lymphoma is an inactive HBsAg carrier. In real life, patients with chronic HBV infection and aggressive lymphomas[8] are at higher risk for antiviral prophylaxis failure, with virus breakthrough likely due to poorer performance status and deeper immunosuppression.[2-5] In this era-to-era comparing

Table 1. Baseline characteristics of analyzed patients

Variables	TDF (n = 39)	LAM (n = 38)	*P*
Age, median (range), y	59.5 (25-81)	61 (21-83)	.64
Sex			
Male	23 (59)	21 (55.3)	.74
Female	16 (41)	17 (44.7)	
Underlying hematological malignancy (DLBCL)	39 (100)	38 (100)	n.v.
Ann Arbor stage*			
Stage III	20 (51.3)	18 (47.4)	.73
Stage IV	19 (48.7)	20 (52.6)	
IPI score†			
1	2 (5.1)	1 (2.6)	.57
2-3	15 (38.5)	15 (39.5)	.92
4-5	22 (56.4)	22 (57.9)	.89
HBV status in the serum at pretreatment			
$HBsAg^+$	39 (100)	38 (100)	n.v.
$HBcAb^+$	32 (82.1)	34 (89.5)	.35
HBV DNA‡ at pretreatment			
$HBV\ DNA^+$	12 (30.7)	14 (36.8)	.57
Median (range), IU/mL	499 (100-948)	483 (100-1800)	.58
Transaminase level			
AST ≤40 IU/L	39 (100)	38 (100)	n.v.
ALT ≤40 IU/L	39 (100)	38 (100)	n.v.
Scheduled induction immune-chemotherapy (R-CHOP-21)	39 (100)	38 (100)	n.v.

Unless otherwise indicated, data are n (%). No patient had hepatitis C or delta or HIV coinfections.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBcAb, hepatitis B core antibody; n.v., not valuable; TDF, tenofovir disoproxil fumarate.

*Stage III is defined as multiple lymph node groups on both sides of the diaphragm; stage IV is defined as multiple extranodal sites or lymph nodes and extranodal disease.[20]

†Five factors were included: age > 60 years, serum lactate dehydrogenase above normal, Eastern Cooperative Oncology Group performance status of 2 to 4, Ann Arbor stage III or IV, and extranodal involvement at >1 site. Each factor gets 1 point, and possible scores range from 0 to 5. A higher score indicates poorer prognosis.[9]

‡By real-time PCR (cutoff = 20 IU/mL).

trial, we analyzed the largest (n = 39 cases) and longest (median follow-up, 6.5 years) prospective series of HBsAg-seropositive patients treated with TDF vs a historic cohort treated with LAM against HBV reactivation following lengthy immune-chemotherapy.[6,7] Of note is the particular homogeneity of the study population in terms of underlying malignant disease (stages III-IV DLBCLs),[8] front-line antineoplastic treatment (R-CHOP-21 scheduled for 6 cycles),[6,7] and duration of PAVP (12 months).[3,4] The risk of HBV reactivation (primary end point) in patients protected with TDF was ~40 percentage points lower (HBV-related acute hepatitis and chemotherapy disruption, 10 and 15 percentage points lower, respectively) compared with LAM, indicating that TDF is clinically very effective.[12] Until now, there are no relevant data on the use of oral nucleos(t)ide analogs with a high genetic barrier to resistance in this setting.[3,4] By systematically reviewing the literature, we found 5 articles on entecavir vs LAM and 3 articles on TDF vs LAM as prophylactic treatment for chronic HBV infection–related complications in a total of 170 $HBsAg^+$ participants scheduled to undergo 6 cycles of R-CHOP-21 induction therapy for B-cell NHL.[13-19] The HBV-related outcomes are reported in Table 2. The median reactivation rates, acute hepatitis, and chemotherapy disruption among the patients in the entecavir arms were 10% (range, 0-12%), 4% (range, 0-6%), and 2% (range, 0-6%), respectively, vs 0%, 0%, and 0% (with ranges of 0-0%), respectively, among the patients in the TDF arms. Thus, TDF had the highest probability (100%) for HBV reactivation and HBV-related acute hepatitis and chemotherapy disruption rate reduction in this cohort of lymphoma patients.[9] Oncologists and hepatologists/infectious disease specialists, who coordinate the management of HBV infection, should be aware of cost-effectiveness. Using Italian data, the total cost of the TDF program was €277 149 compared with €40 424 for the LAM cohort. However, if the additional costs of reactivations, acute hepatitis, and retreatment with a new antiviral drug in the LAM cohort are considered, the cost of the TDF approach was ~1.69-fold higher than treatment with LAM. Altogether, these data suggest that the TDF-driven strategy may be more effective than a LAM-driven strategy in the prevention of HBV reactivation and its related morbidity for patients with chronic HBV infection undergoing repeated courses of immune-chemotherapy for B-cell lymphomas.[6,7] Larger studies are needed to demonstrate a survival advantage from PAVP with TDF in patients with advanced-stage DLBCL[20] and adverse IPI scores.[9]

Table 2. Outcomes reported for TDF and entecavir as primary antiviral prophylaxis in patients with chronic HBV infection scheduled to receive 6 cycles of R-CHOP-21 for NHL in Ann Arbor stages III or IV

Study	Type of study	No. of patients	Hematological malignancy	HBV status (percentage of patients)	Antiviral prophylaxis	Follow-up median, mo	Outcomes reported
This study	Prospective	39	DLBCL	$HBsAg^+$ (100)	TDF	78	HBV reactivations, 0%
				$HBV\ DNA^+$ (31)			HBV-related hepatitis, 0%
							Chemotherapy disruptions, 0%
Gentile et al[14]	Prospective	11	Aggressive NHL*	$HBsAg^+$ (100)	TDF	24	HBV reactivations, 0%
				$HBV\ DNA^+$ (NA)			HBV-related hepatitis, 0%
							Chemotherapy disruptions, 0%
Choi et al[16]	Retrospective	9	Aggressive NHL*	$HBsAg^+$ (100)	TDF	16	HBV reactivations, 0%
				$HBV\ DNA^+$ (100)			HBV-related hepatitis, 0%
							Chemotherapy disruptions, 0%
Koskinas et al[15]	Prospective	4	Aggressive NHL*	$HBsAg^+$ (100)	TDF	18	HBV reactivations, 0%
				$HBV\ DNA^+$ (100)			HBV-related hepatitis, 0%
							Chemotherapy disruptions, 0%
Huang et al[13]	Randomized	38	DLBCL	$HBsAg^+$ (100)	Entecavir	40	HBV reactivations, 10%
				$HBV\ DNA^+$ (NA)			HBV-related hepatitis, 0%
							Chemotherapy disruptions, 2.6%
Choi et al, 2014[16]	Retrospective	25	Aggressive NHL*	$HBsAg^+$ (100)	Entecavir	16	HBV reactivations, 12%
				$HBV\ DNA^+$ (NA)			HBV-related hepatitis, 6%
							Chemotherapy disruptions, 2%
Li et al[17]	Retrospective	24	Aggressive NHL*	$HBsAg^+$ (100)	Entecavir	NA	HBV reactivations, 12%
				$HBV\ DNA^+$ (83)			HBV-related hepatitis, 6%
							Chemotherapy disruptions, 6%
Kim et al[18]	Prospective	16	DLBCL	$HBsAg^+$ (100)	Entecavir	16	HBV reactivations, 6%
				$HBV\ DNA^+$ (100)			HBV-related hepatitis, 4%
							Chemotherapy disruptions, 0%
Chen et al[19]	Retrospective	4	Aggressive NHL*	$HBsAg^+$ (100)	Entecavir	36	HBV reactivations, 0%
				$HBV\ DNA^+$ (50)			HBV-related hepatitis, 0%
							Chemotherapy disruptions, 0%

PubMed, Embase, and Cochrane library databases were searched for articles up to 31 March 2010. All data included in this table are personal extrapolations by the authors based on the features available in each report.

NA, not applicable.

*B-cell NHL, not otherwise specified.

Authorship

Contribution: M.P. designed the research; M.P., R.D.P., C.G., and N.P. performed the research and wrote the manuscript; I.Z., C.M., F.T., A.G., M.L., M.D.P., and M.R. collected data; N.P. analyzed data; C.S. worked on the cost analysis; and F.P. and M.P. performed the final revision of the manuscript.

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ORCID profiles: M.P., 0000-0001-8508-2524; R.D.P., 0000-0001-5641-231X; C.G., 0000-0003-3943-4263; I.Z., 0000-0002-1603-8930; N.P., 0000-0002-2714-5109; C.M., 0000-0002-4984-9238; F.T., 0000-0001-6929-0729; A.G., 0000-0001-7143-6758; M.L., 0000-0002-9408-4633; M.D.P., 0000-0003-2977-0634; M.R., 0000-0002-5845-3446; C.S., 0000-0002-7032-4989; F.P., 0000-0003-2563-4125.

Correspondence: Roberta Della Pepa, Department of Clinical Medicine and Surgery, Federico II University Medical School, Via S. Pansini 5, 80131 Naples, Italy; e-mail: roberta.dellapepa@unina.it

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