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Severe Acute Exacerbation After Cessation of Nucleos(t)ide Analog for Chronic Hepatitis B: A Real-World Study of Routine Practice

There is an ongoing debate as to whether patients with chronic hepatitis B (CHB) may discontinue nucleos(t)ide analogue (NA) therapy before seroclearance of hepatitis B surface antigen (HBsAg).[1] Whereas treatment discontinuation may facilitate HBsAg seroclearance and avoid indefinite drug exposure,[2] reactivation of viral replication almost always follows treatment cessation and frequently leads to clinical flares.[3] In patients who encounter withdrawal flares, severe acute exacerbation (SAE) could occur with fatal consequences.[4] Quantitative knowledge about the risk of SAE is imperative to inform the debate and also the practice.

We set out to quantify the incidence of SAE and explore associated risk factors in a real-world cohort of consecutive patients who discontinued NA therapy in their routine clinical care. We systematically searched the electronic health care records of all adults with CHB treated with any approved NA regimen from April 1, 2004 to October 8, 2020 in the E-Da Healthcare System. Key eligibility criteria included cessation of NA treatment after being treated for longer than 1 year, positive HBsAg and negative HBeAg at treatment cessation, and absence of any malignancy. The main reason for treatment discontinuation was loss of reimbursement coverage according to the National Health Insurance and patients were not selected by particular stopping rules. Eligible patients were observed for occurrence of SAE, which was defined by serum alanine transaminase >5 times the upper limit of normal (40 U/L by the local standard) plus bilirubinemia >2 mg/dL. Further details of the method are available in the Supplementary Methods.

After screening a total of 5452 consecutive patients with CHB treated with NA therapy, we found 830 of them eligible. Their characteristics are summarized in Supplementary Table 1. Briefly, most were treated with entecavir or tenofovir disoproxil fumarate for a median duration of 34.7 (interquartile range [IQR], 18.4–35.9) months. Liver cirrhosis was diagnosed in 97 (11.7%) patients at treatment initiation. Treatment was resumed in 325 patients with a cumulative retreatment rate of 55.55% (95% confidence interval [CI], 49.50%–61.80%) at 10 years.

SAE occurred in 38 patients during 3322 person-years of observation (Figure 1*A*), yielding an average annual rate of 1.14% (95% CI, 0.81%–1.57%) and a 10-year cumulative incidence of 6.6% (95% CI, 4.7%–9.2%). Notably, the annual SAE incidence rate was significantly higher in the first 2 years (1.84%; 95% CI, 1.20%–2.70%) than afterward (0.63%; 95% CI, 0.32–1.10; $P = .002$). Moreover, the risk significantly differed by the presence of cirrhosis at treatment initiation (Figure 1*B*). The 10-year cumulative incidences of SAE were 19.10% (95% CI, 10.1%–34.4%) and 5.2% (95% CI, 3.5%–7.8%) in patients with and without cirrhosis, respectively ($P = .0002$). In the multivariable Cox proportional hazards model, liver cirrhosis (adjusted hazard ratio, 3.63; 95% CI, 1.80%–7.33; $P < .001$) and male sex (adjusted hazard ratio, 2.81; 95% CI, 1.0%–7.93; $P = .05$) were factors associated with a significantly higher SAE risk (Supplementary Table 2).

The median duration from treatment cessation to occurrence of SAE was 16.3 (IQR, 9.0–25.7) months, but could be as short as 2.8 months. At SAE, the median alanine transaminase level was 493 (IQR, 257–1018) U/L with a highest value of 2563 U/L, and the median serum bilirubin was 2.59 (IQR, 2.24–4.73) mg/dL with a highest value of 19.22 mg/dL. Despite retreatment, 7 of the 38 (18.4%) patients with SAE progressed to acute on chronic liver failure and 3 (7.9%) subsequently died. Of note, cirrhosis was present in 3 of the 7 patients with acute on chronic liver failure and 2 of the 3 mortality cases. We also conducted a sensitivity test in the subgroup treated with either entecavir or tenofovir disoproxil fumarate monotherapy (n = 665) and found consistent results (data not shown).

Therefore, our analysis quantified the risk of SAE using time-to-event data from patients with CHB who stopped treatment as part of their routine care in a real-world setting. A higher risk within the first 2 years off treatment seemed in line with the chronologic pattern of clinical relapse noted in previous studies.[5,6] These data may help tailor the surveillance program for patients who stop NA treatment. Nonetheless, the underlying mechanism remained elusive. Presumably, antiviral immunity is more intense in the face of abrupt viral reactivation than in a relatively stable state,[7] and thus flares could be more severe right after removal of viral inhibition. More research is warranted to elucidate the reason for a declining incidence of SAE over time.

Our data also demonstrated that liver cirrhosis and male sex were associated with a higher SAE risk. Most concerning for the occurrence of SAE was a high rate of

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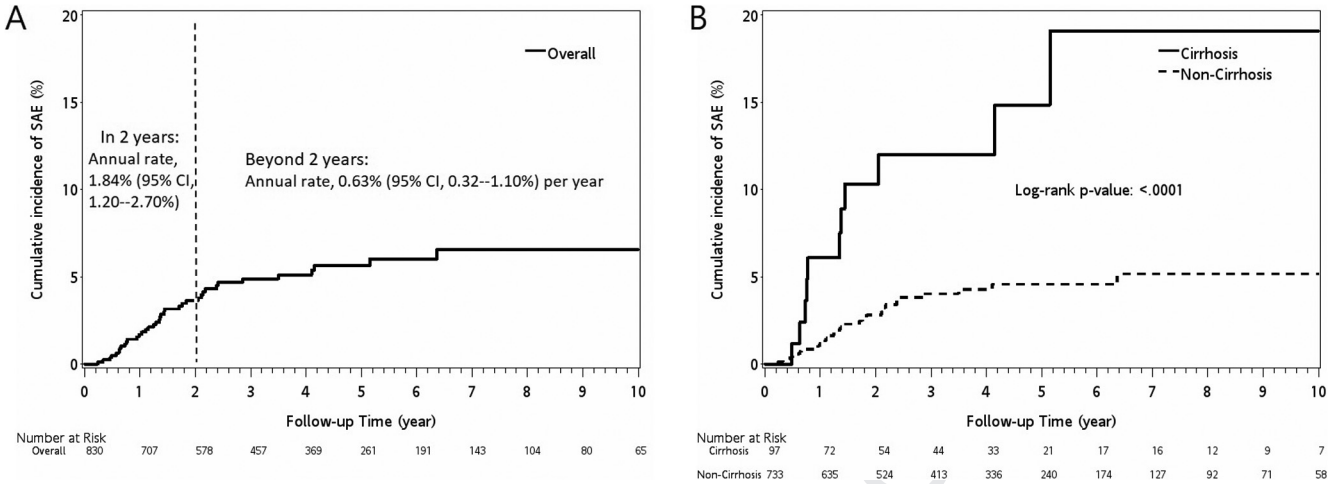

Figure 1. The cumulative incidence of SAE following cessation of antiviral treatment in the overall study population (*A*) and in the subgroups stratified by liver cirrhosis at treatment imitation (*B*).

progression to acute on chronic liver failure (18%) and death (8%) despite retreatment, particularly in patients with cirrhosis. In accordance with our observation, a prospective cohort study also from Taiwan reported that 7 of 691 patients (1.01%) developed hepatic decompensation following treatment cessation and 3 of them died. Notably, all of the 7 patients had cirrhosis.[8] In view of the excessive risk and a potentially irreversible course of SAE, it is inadvisable to suggest treatment cessation in patients with cirrhosis. We believe the practice of finite NA therapy should be based on accurate risk stratification and shared decision making. Emerging data indicated that convenient biomarkers, such as serum HBsAg and/or hepatitis B core-related antigen titers, along with clinical information may help resolve the conundrum between the risk of clinical flares and chance of HBsAg clearance.[9,10]

This study was limited by factors inherent in retrospective research, such as missing data. For instance, data for the evaluation of remnant fibrosis were far less complete at treatment cessation than at initiation. Additionally, the number of SAE events might limit the exploration of risk factors beyond cirrhosis and sex. The number of patients with cirrhosis was also statistically underpowered to look for risk factors within this subgroup. Finally, caution is warranted before generalizing our findings. For example, this study did not include patients presenting with compensated cirrhosis and hepatitis B virus viremia <2000 IU/mL, who should have received treatment in other countries.

In conclusion, patients with CHB should be informed of potential SAE risks as shown in our analysis before stopping NA treatment.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://doi.org/10.1016/j.cgh.2012.11.00.

Y.-C. HSU Q8
Center for Liver Diseases, E-Da Hospital
Kaohsiung, Taiwan

School of Medicine, College of Medicine
I-Shou University
Kaohsiung, Taiwan

Department of Internal Medicine
Fu-Jen Catholic University Hospital
New Taipei, Taiwan

Institute of Biomedical Informatics
National Yang Ming Chiao Tung University
Taipei, Taiwan

Graduate Institute of Clinical Medical Science
China Medical University
Taichung, Taiwan

J.-L. WU
Department of Public Health
National Cheng Kung University, College of Medicine
Tainan, Taiwan

C.-H. TSENG
School of Medicine, College of Medicine
I-Shou University
Division of Gastroenterology and Hepatology
Department of Medicine
E-Da Cancer Hospital
Kaohsiung, Taiwan

M.H. NGUYEN
Division of Gastroenterology and Hepatology
Stanford University Medical Center
Department of Epidemiology and Population Health
Stanford University Medical Center
Palo Alto, California

C.-W. LIN
School of Medicine, College of Medicine
I-Shou University
Division of Gastroenterology and Hepatology
E-Da Dachang Hospital
Kaohsiung, Taiwan

C.-L. HUNG
Administrative Center
E-Da Healthcare System
Kaohsiung, Taiwan

References

1. Terrault NA, et al. Hepatology 2018;67:1560–1599.
2. Berg T, et al. J Hepatol 2017;67:918–924.
3. Seto WK, et al. Gut 2015;64:667–672.
4. Van Hees S, et al. Aliment Pharmacol Ther 2018;47:1170–1180.
5. Hsu YC, et al. Clin Gastroenterol Hepatol 2016;14:1490–1498.
6. Chiu SM, et al. Clin Gastroenterol Hepatol 2020;18:2989–2997.
7. Shi Y, et al. BMJ 2020;370:m2200.
8. Jeng WJ, et al. Hepatology 2018;68:425–434.
9. Hsu YC, et al. Aliment Pharmacol Ther 2019;49:107–115.
10. Sonneveld MJ, et al. Clin Gastroenterol Hepatol 2020.

Reprint requests
Address requests for reprints to: Yao-Chun Hsu, MD, PhD, Center for Liver Diseases, E-Da Hospital, I-Shou University, No. 1, Yida Road, Yanchao District, Kaohsiung 82445, Taiwan. e-mail: holdenhsu@gmail.com. Q3

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Conflicts of interest
These authors disclose the following: Yao-Chun Hsu has received lecture fees from AbbVie, Bristol-Myers Squibb, Gilead Sciences, and Novartis; and served as an advisory committee member for Gilead Sciences. Cheng-Hao Tseng has received lecture fees from AbbVie, Bristol-Myers Squibb, Gilead Sciences, Bayer, and Roche. Mindie H. Nguyen has received research support from Pfizer, Gilead Sciences, Enanta, Vir Biotech, Glycotests, B. K. Kee Foundation, Helio Health, and the National Cancer Institute; and has served as an advisory board member or consultant for Gilead, Intercept, Novartis, Eisai, Bayer, Exact Science, Laboratory of Advanced Medicine, Spring Bank, and Janssen. The remaining authors disclose no conflicts. Q5

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Supplementary Methods

We retrospectively screened the electronic health care records of all patients who received any NA regimen for CHB between April 1, 2004 and October 8, 2020 in the E-Da Hospital, E-Da Cancer Hospital, and E-Da Dachang Hospital. Data were extracted from the EDA Healthcare System electronic health care records database and complimented by manual chart review as needed. The study was approved by the institutional review board of the E-Da Healthcare System (EMRP-108-058).

Eligibility required age ≥20 years, CHB infection ≥6 months, and NA therapy for at least 1 year before treatment cessation. Exclusion criteria included HBsAg clearance or positive hepatitis B e antigen serology at treatment cessation, hepatitis C virus coinfection, organ transplantation, or any malignancy. Cirrhosis was defined mainly by a clinical diagnosis, usually based on noninvasive assessments. Hepatic insufficiency was defined by serum bilirubin ≥2 mg/dL or prolongation of prothrombin time ≥3 seconds because such operational definition indicated reimbursement for antiviral treatment according to the National Health Insurance.

Antiviral therapy for CHB was regulated by the National Health Insurance with specified reimbursement criteria. Except for a special condition, such as hepatic insufficiency, organ transplantation, or malignancy, the indications were generally determined by high viral load (≥2000 IU/mL) and persistent alanine transaminase (ALT) elevation (>2 times the upper limits of normal for at least 3 months), with details separated by hepatitis B e antigen status. For the indication of cirrhosis, a prerequisite of hepatitis B virus DNA ≥2000 IU/mL was required during the study period.

The reimbursement was finite in principle and generally 3 years at most. After July 1, 2010, indefinite coverage was granted for the indication of cirrhosis but required evidence of portal hypertension (ie, splenomegaly or esophagogastric varices) if pathologic proof was absent. Accordingly, patients with a clinical diagnosis of cirrhosis who did not present with viremia ≥2000 IU/mL or overt features of portal hypertension did not qualify for indefinite reimbursement and still had to stop treatment throughout the study period.

The reimbursement criteria for retreatment were similar to those for treatment initiation. Retreatment was not indicated for virologic relapse alone or transient (<3 months) ALT elevation, regardless of the level of serum hepatitis B virus DNA or ALT.

The primary outcome was SAE, defined by abrupt elevation of serum ALT >5 times upper limits of normal (the conventional upper limits of normal of 40 U/L) plus bilirubinemia >2 mg/dL. Acute on chronic liver failure was defined by serum bilirubin ≥5 mg/dL and international normalized ratio ≥1.5, accompanied with clinical complications, such as ascites or encephalopathy within 4 weeks.

The cumulative incidences were calculated by the Kaplan-Meier method and the differences examined by the log-rank test. The incidence rates were calculated by event per person-time and the chronologic trend was examined using Poisson regression. The Cox proportional hazards model was performed in a backward manner to eliminate nonsignificant variables. Point estimates were reported along with 95% confidence intervals. All statistical examinations were 2-sided with significance set at a P value $< .05$. A commercially available software SAS version 9.4 (SAS Institute, Cary, NC) was used for the analysis.

Supplementary Table 1. Characteristics of the Study Cohort

Characteristics[a]	All (n = 830)
Biologic sex, n (%)	
Female	207 (24.9)
Male	623 (75.1)
Age, *y*	49.5 (40.5–57.2)
Body mass index, kg/m^2	24.3 (21.9–26.8)
Diabetes mellitus, n (%)	30 (3.6)
Hypertension, n (%)	164 (19.8)
Dyslipidemia, n (%)	171 (20.6)
AST, *U/L*	29.0 (24.0–38.0)
ALT, *U/L*	27.0 (20.0–41.0)
Bilirubin, *mg/dL*	1.1 (0.8–1.5)
Creatinine, *mg/dL*	1.1 (1.0–1.3)
Prothrombin time, *s*	10.6 (10.3–11.4)
International normalized ratio	1.0 (1.0–1.1)
White blood cell count, $10^3/\mu L$	5.7 (4.6–6.8)
Hemoglobin, *g/dL*	14.6 (12.8–15.7)
Platelet count, $10^3/\mu L$	188 (139–229)
Antiviral regimen, n (%)	
Lamivudine	109 (13.1)
Adefovir	30 (3.6)
Telbivudine	26 (3.1)
Entecavir	456 (54.9)
TDF	209 (25.2)
Duration on therapy, *mo*	34.7 (18.4–35.9)
Pretreatment cirrhosis, n (%)[b]	97 (11.7)
Pretreatment hepatic insufficiency, n (%)[a]	256 (30.8)
Pretreatment positive HBeAg, n (%)	225 (27.1)
Pretreatment positive anti-HBe, n (%)	473 (57.0)
Pretreatment HBV DNA, *log IU/mL*	6.3 (4.7–8.3)
Pretreatment AST, *U/L*	91.0 (54.0–202.0)
Pretreatment ALT, *U/L*	128 (68.0–364.0)

NOTE. The characteristics were summarized at treatment cessation unless the pretreatment status was specified, and were expressed as number (percentage) or median (interquartile range).
ALT, alanine transaminase; anti-HBe, hepatitis B e antibody; AST, aspartate transaminase; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; TDF, tenofovir disoproxil fumarate.
[a]Hepatic insufficiency was defined by laboratory measurements of serum bilirubin ≥2 mg/dL or prolongation of prothrombin time ≥3 seconds because this operational definition indicated reimbursement for antiviral treatment according to the national health insurance in Taiwan.
[b]Cirrhosis was defined by a clinical diagnosis based on clinical assessment including liver images.

Supplementary Table 2. Cox Proportional Hazards Regression to Explore Factors Associated With Severe Acute Exacerbation

	Univariable analysis			Multivariable analysis		
	HR	95% CI	*P* value	aHR	95% CI	*P* value
Age, *y*	1.02	0.99–1.04	.25			
Male sex	2.86	1.02–8.07	.05	2.81	1.0–7.93	.05
Body mass index, kg/m^2	1.05	0.96–1.15	.32			
AST, per 100 U/L	1.25	0.43–3.65	.68			
ALT, per 100 U/L	1.29	0.53–3.12	.57			
Antiviral regimen, n						
Entecavir vs older drugs	0.53	0.26–1.05	.07			
TDF vs older drugs	0.36	0.13–1.01	.06			
Duration on therapy, *mo*	1.0	0.98–1.02	.86			
Pretreatment cirrhosis	3.68	1.82–7.42	< .001	3.63	1.80–7.33	< .001
Pretreatment liver insufficiency	2.0	1.05–3.79	.03			
Pretreatment positive HBeAg	1.15	0.58–2.29	.68			
Pretreatment positive anti-HBe	1.11	0.47–2.60	.82			
Pretreatment HBV DNA, *log IU/mL*	1.04	0.88–1.23	.66			
Pretreatment AST, 100 U/L	1.04	0.99–1.10	.11			
Pretreatment ALT, 100 U/L	1.02	0.98–1.07	.34			

NOTE. Measured at treatment cessation unless otherwise specified as "pretreatment."
aHR, adjusted hazard ratio; ALT, alanine transaminase; anti-HBe, hepatitis B e antibody; AST, aspartate transaminase; CI, confidence interval; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HR, hazard ratio; TDF, tenofovir disoproxil fumarate.