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Editorial Board Member of *World Journal of Hepatology*, Jonathan Soldera, MSc, MD, Professor Gastroenterology and Acute Medicine, University of South Wales, Cardiff, CF37 1DL, United Kingdom. jonathansoldera@gmail.com

AIMS AND SCOPE

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ORIGINAL ARTICLE

Retrospective Cohort Study

Tenofovir alafenamide significantly increased serum lipid levels compared with entecavir therapy in chronic hepatitis B virus patients

Rui-Min Lai, Shan Lin, Miao-Miao Wang, Na Li, Jia-Hui Zhou, Xiao-Yu Lin, Tian-Bin Chen, Yue-Yong Zhu, Qi Zheng

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Rui-Min Lai, Shan Lin, Na Li, Jia-Hui Zhou, Xiao-Yu Lin, Yue-Yong Zhu, Qi Zheng, Department of Hepatology, Hepatology Research Institute, The First Affiliated Hospital, Fujian Medical University, Fujian Clinical Research Center for Hepatopathy and Intestinal Diseases, Fuzhou 350005, Fujian Province, China

Rui-Min Lai, Qi Zheng, Department of Hepatology, National Regional Medical Center, Binhai Campus of the First Affiliated Hospital, Fujian Medical University, Fuzhou 350212, Fujian Province, China

Miao-Miao Wang, Department of Endocrinology, The 910th Hospital of The Joint Service Support Force, Quanzhou 362000, Fujian Province, China

Tian-Bin Chen, Department of Laboratory Medicine, The First Affiliated Hospital, Fujian Medical University, Fuzhou 350005, Fujian Province, China

Corresponding author: Qi Zheng, PhD, Chief Physician, Professor, Department of Hepatology, Hepatology Research Institute, The First Affiliated Hospital, Fujian Medical University, Fujian Clinical Research Center for Hepatopathy and Intestinal Diseases, No. 20 Chazhong Road, Taijiang District, Fuzhou 350005, Fujian Province, China. bei0825@163.com

Abstract

BACKGROUND

Tenofovir alafenamide (TAF) has a serum lipid-raising effect in patients with HIV; however, its effect on serum lipids and nonalcoholic fatty liver disease (NAFLD) risk in patients with chronic hepatitis B (CHB) is unclear.

AIM

To compare the effects of TAF and entecavir (ETV) on serum lipid levels in patients with CHB.

METHODS

In this retrospective cohort study, the data including the clinical features, serum lipids, and metabolic factors of patients with CHB at baseline and approximately 1 year after TAF or ETV treatment were collected and analyzed. We used propensity score-matched models to assess the effects on high-density lipoprotein, low-density lipoprotein, triglycerides, and total cholesterol (TCHO).

RESULTS

A total of 336 patients (75.60% male) were included; 63.69% received TAF and 36.31% received ETV. Compared with the ETV group, the TAF group had significantly higher TCHO levels after treatment (4.67 ± 0.90 *vs* 4.36 ± 1.05, $P = 0.006$). In a propensity score-matched model for body mass index, age, sex, smoking, drinking, presence of comorbidities such as NAFLD, cirrhosis, diabetes mellitus, and hypertension, TAF-treated patients had significantly increased TCHO levels compared to that at baseline ($P = 0.019$). There was no difference for the ETV group. Body mass index, sex, hypertension, baseline TCHO, and creatine kinase-MB isoenzyme levels were significantly associated with elevated TCHO levels in logistic regression analysis. However, 1-year TAF treatment did not increase the incidence of NAFLD.

CONCLUSION

A greater increase in TCHO was observed in patients with CHB receiving TAF compared to those receiving ETV. However, TAF-induced dyslipidemia did not increase the incidence of NAFLD.

Key Words: Tenofovir alafenamide; Entecavir; Hepatitis B virus; Serum lipid; Metabolic factor

Core Tip: This study compared the effects of tenofovir alafenamide (TAF) and entecavir on serum lipid levels in chronic hepatitis B patients. The results suggested that TAF-treated patients had significantly increased triglycerides, and total cholesterol levels compared to that at baseline, while there was no difference in the entecavir group. However, dyslipidemia caused by TAF therapy did not increase the incidence of nonalcoholic fatty liver disease. Our findings indicated that the potential impact of anti-viral therapy on the lipid profile may be an important consideration in the treatment choices for chronic hepatitis B patients with abnormal metabolic factors.

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INTRODUCTION

Hepatitis B virus (HBV) infects approximately 240 million people worldwide, including approximately 86 million people in China[1]. Chronic hepatitis B (CHB) may lead to decompensation of cirrhosis and hepatocellular carcinoma (HCC), which are the leading causes of mortality in patients with CHB[2]. Nonalcoholic fatty liver disease (NAFLD) is a hepatic manifestation of metabolic syndrome (MetS), with a cumulative prevalence of 24% worldwide[3]. In recent decades, the prevalence of NAFLD has significantly increased in China, leading to the coexistence of NAFLD and CHB. Dyslipidemia, which is characterized by high triglyceride (TG), high total cholesterol (TCHO), low high-density lipoprotein (HDL), and high low-density lipoprotein levels, is strongly associated with NAFLD and MetS[4].

Interferon and nucleoside analog therapies cannot completely eradicate HBV infection[5]. Many patients require long-term anti-HBV therapy with potent oral drugs tenofovir alafenamide (TAF) and entecavir (ETV), which are recommended as first-line treatment in HBV clinical practice guidelines[6]. TAF has also recently been incorporated into antiretroviral regimens for people with HIV, and we observed its impact on serum lipid levels in these individuals. A prospective cohort study showed that patients with HIV infection treated with a TAF-containing regimen had significantly worse blood lipid levels, especially those with higher LDL and TCHO[7]. In a recent real-world study, switching from tenofovir disoproxil fumarate (TDF) to a TAF-containing regimen in HIV-infected patients resulted in a significant increase in serum lipid profiles[8]. However, data on the effects of TAF on serum lipid levels in patients with HIV may be limited by the potentially confounding effects of concomitant antiretroviral HIV drugs.

The effect of ETV on serum lipid profiles has not yet been reported in postmarketing studies. A retrospective cohort study showed greater reductions in TCHO, LDL, and HDL levels in patients with CHB treated with TDF than in those treated with ETV[9]. TAF is considered the successor of TDF; however, no studies have compared the effects of TAF and ETV on lipid profiles in HBV-treated patients. Meanwhile, there are limited data on the effects of TAF on metabolism-related complications in real-world settings. Therefore, this retrospective cohort study aimed to characterize the effect of TAF on serum lipid levels and NAFLD risk in patients with CHB, and we compared the pretreatment and post-treatment serum lipid profile changes after initiation of either TAF or ETV anti-viral therapy.

MATERIALS AND METHODS

Eligibility/study subjects

This study included all patients with CHB older than 18 years who visited the outpatient department of the Hepatology Research Institute of the First Affiliated Hospital of Fujian Medical University between January 2020 and January 2021. Information such as patient demographics, treatment history, laboratory data, and comorbidities was extracted from the electronic medical record system. CHB was defined according to the Guidelines for the Prevention and Treatment of Chronic Hepatitis B (2019) of China[10]. Diagnosis of decompensated cirrhosis was confirmed by ultrasonography or imaging for inclusion in the study. Finally, the study included 336 participants (Figure 1) who were taking TAF or ETV and had a pretreatment serum lipid profile and repeated serum lipid assessment after initiating anti-viral therapy for 1 year. Exclusion criteria were as follows: (1) Less than 1 year of anti-viral therapy; (2) Use of other oral anti-viral drugs during the study period; (3) Use of lipid-lowering drugs; (4) Complicated with other liver disease or pregnancy; (5) Heavy alcohol intake (amounting to ethanol consumption of ≥ 40 g/day for males and ≥ 20 g/day for females).

Measurement of parameters /data collection

The collected clinical and demographic data included age, sex, body mass index (BMI), drinking and smoking habits, date of anti-viral treatment initiation, cirrhosis, and comorbidities [diabetes mellitus (DM), hypertension, and NAFLD]. A fatty liver was identified using ultrasonography. Clinical laboratory information included HBV-DNA, hepatitis B surface antigen, aspartate aminotransferase, alanine aminotransferase, glomerular filtration rate, uric acid, creatinine, creatine kinase (CK), CK-MB isoenzyme, fasting serum lipid profiles (TCHO, TG, HDL, and LDL), and baseline fasting blood glucose levels. The parameters were measured by the clinical laboratory of the First Affiliated Hospital of Fujian Medical University, and data were collected before and 1 year after the initiation of anti-viral therapy. This retrospective study was approved by the Ethics Committee of the First Affiliated Hospital of Fujian Medical University, China.

Statistical analysis

Statistical analyses were performed using SPSS 23.0. Normally distributed continuous variables were presented as mean ± standard deviation, which were further evaluated by Student's *t*-test for the different treatment groups. Categorical variables were described using frequencies and proportions, and Pearson's χ^2 test was used to compare categorical variables. The paired *t*-test and McNemar's test were used to assess the differences between the levels before and after treatments in the same treatment group. We calculated the pretreatment and post-treatment differences in each lipid profile component in order to evaluate the impact of anti-viral therapy on lipid profile.

Propensity score-matched models were used to assess the effect of treatment type (TAF *vs* ETV) on lipid profile component changes. All propensity score-matched models were adjusted for BMI, age, sex, fatty liver disease, cirrhosis, DM, hypertension, smoking, and drinking. We presented the average changes in the model coefficients. Finally, logistic regression analysis was used to estimate the odds ratio of the association between baseline factors and elevated TCHO levels. Statistical *P* values less than 0.05 were considered significant.

RESULTS

Summary of baseline clinical and demographic data of TAF-treated and ETV-treated CHB patients

Overall, 336 CHB patients receiving anti-viral therapy (TAF, n = 214 *vs* ETV, n = 122) were included in the study. The mean age was 46.67 years, 75.60% were male, and 30.95% were cirrhotic at baseline. Patients were older in the ETV group (P = 0.001), but the two groups had a similar rate of NAFLD (TAF: 35.05% *vs* ETV: 26.23%, P = 0.122) and BMI (TAF: 22.97 *vs* ETV: 23.78, P = 0.152). However, hypertension and cirrhosis were more prevalent in the ETV group (17.21% *vs* 7.94%, P = 0.016 and 40.98% *vs* 25.23%, P = 0.004, respectively). TAF and ETV had similar levels of hepatitis B surface antigen (3.07 *vs* 3.04, P = 0.787) and HBV-DNA (1.94 *vs* 1.86, P = 0.560) (Table 1) as well as no statistically significant differences in serum alanine aminotransferase and aspartate aminotransferase levels.

Comparison of serum lipid profiles before and after anti-viral therapy in TAF-treated vs ETV-treated CHB patients

TCHO, TG, LDL, and HDL values in the TAF-treated and ETV-treated individuals were comparable at baseline (prior to anti-viral medication). In the TAF-treated group, post-treatment serum lipoprotein levels were considerably higher than the pretreatment levels for TCHO (4.51 ± 0.93 *vs* 4.67 ± 0.90, P = 0.001) and TG (1.25 ± 0.67 *vs* 1.37 ± 0.81, P = 0.014), whereas HDL and LDL levels did not change in the TAF group over the duration of our study. Further, the TAF group showed significantly higher post-treatment TCHO levels compared with that in the ETV group (4.67 ± 0.90 *vs* 4.36 ± 1.05, P = 0.006). However, TAF treatment did not increase the incidence of NAFLD after 1 year of follow-up (Table 2). In the ETV cohort, there was no significant difference between the pretreatment and post-treatment serum lipoprotein levels.

TAF as an independent predictor of TCHO level change

Using propensity score-matched models for BMI, age, sex, smoking, drinking, and presence of comorbidities such as NAFLD, cirrhosis, DM, and hypertension, we assessed the impact of TAF compared to ETV on achieving an increase in the levels of the serum lipid profile (Table 3). Patients treated with TAF had a statistically significant increase in TCHO levels (P = 0.019), which was 5% higher than that in the baseline lipid profile.

Table 1 Summary of demographic and clinical characteristics at baseline of chronic hepatitis B patients on tenofovir alafenamide or entecavir therapy

Characteristic	TAF, *n* = 214	ETV, *n* = 122	*P* value
Age in yr	43.38 ± 10.42	49.96 ± 11.82	0.001
Male	158 (73.83)	96 (78.69)	0.387
BMI in kg/m^2	22.97 ± 2.93	23.78 ± 3.30	0.152
Smoking	16 (7.48)	15 (12.30)	0.203
Drinking	13 (6.07)	14 (11.48)	0.123
ALT in U/L	36.60 ± 36.87	30.44 ± 20.00	0.089
AST in U/L	28.01 ± 26.41	24.50 ± 13.58	0.172
logHBsAg in ng/mL	3.07 ± 0.92	3.04 ± 0.84	0.787
logDNA in IU/mL	1.94 ± 1.23	1.86 ± 1.05	0.56
CREA in μmol/L	73.68 ± 15.87	74.82 ± 16.78	0.535
UA in μmol/L	353.52 ± 89.10	357.23 ± 84.29	0.708
GFR in mL/min	103.48 ± 15.01	97.86 ± 14.17	0.001
CK in U/L	157.23 ± 444.75	122.91 ± 71.31	0.401
FBG in mmol/L	5.18 ± 0.80	5.52 ± 1.61	0.011
Concurrent diseases			
Hypertension	17 (7.94)	21 (17.21)	0.016
DM	20 (9.35)	13 (10.66)	0.844
NAFLD	75 (35.05)	32 (26.23)	0.122
Cirrhosis	54 (25.23)	50 (40.98)	0.004

Data are presented as *n* (%). ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; CK: Creatine kinase; CREA: Creatinine; DM: Diabetes mellitus; ETV: Entecavir; FBG: Fasting blood-glucose; GFR: Glomerular filtration rate; HBsAg: Hepatitis B surface antigen; NAFLD: nonalcoholic fatty liver disease; TAF: Tenofovir alafenamide; UA: Uric acid.

Table 2 Comparison of serum lipid profile before and after 1 year of anti-viral therapy either tenofovir alafenamide or entecavir

Characteristic	TAF, *n* = 214, statistic	*P* value[1]	ETV, *n* = 122, statistic	*P* value[1]	*P* value[2]
Pre-Tx TCHO in mmol/L	4.51 ± 0.93	0.001	4.41 ± 1.03	0.275	0.376
Post-Tx TCHO in mmol/L	4.67 ± 0.90		4.36 ± 1.05		0.006
Pre-Tx TG in mmol/L	1.25 ± 0.67	0.014	1.33 ± 0.75	0.052	0.35
Post-Tx TG in mmol/L	1.37 ± 0.81		1.24 ± 0.61		0.126
Pre-Tx HDL in mmol/L	1.32 ± 0.40	0.794	1.26 ± 0.40	0.879	0.246
Post-Tx HDL in mmol/L	1.32 ± 0.36		1.27 ± 0.41		0.285
Pre-Tx LDL in mmol/L	3.12 ± 0.90	0.785	3.06 ± 1.01	0.078	0.543
Post-Tx LDL in mmol/L	3.14 ± 0.92		3.15 ± 1.00		0.906
Pre-Tx NAFLD	75 (35.05)	0.125	32 (26.23)	1	0.122
Post-Tx NAFLD	70 (32.71)		31 (25.41)		0.16

[1]Comparing the pretreatment and post-treatment variables (paired) in each therapy type.
[2]Comparing the same variable (either pretreatment or post-treatment) according to type of therapy. ETV: Entecavir; HDL: High density lipoprotein; LDL: Low-density lipoprotein; NAFLD: Nonalcoholic fatty liver disease; TAF: Tenofovir alafenamide; TCHO: Total cholesterol; TG: Triglycerides; Tx: Treatment.

Table 3 Impact of tenofovir alafenamide on achieving a higher level of total cholesterol in chronic hepatitis B patients

Characteristic	TCHO, increased change (%) by using TAF compared with ETV[1,2], OR (95%CI)	*P* value
5% higher than baseline	1.88 (1.11, 3.16)	0.019
10% higher than baseline	1.70 (0.94, 3.09)	0.081
15% higher than baseline	2.07 (0.99, 4.34)	0.055

[1]All propensity score-matched models were adjusted for body mass index, age, sex, nonalcoholic fatty liver disease, cirrhosis, diabetes mellitus, hypertension, smoking, and drinking. The increased percentage change was presented by using tenofovir alafenamide (TAF) compared with entecavir (ETV).

[2]The increased change was transformation of the treatment effect coefficients in propensity score-matched models. CI: Confidence interval; OR: Odds ratio; TCHO: Total cholesterol.

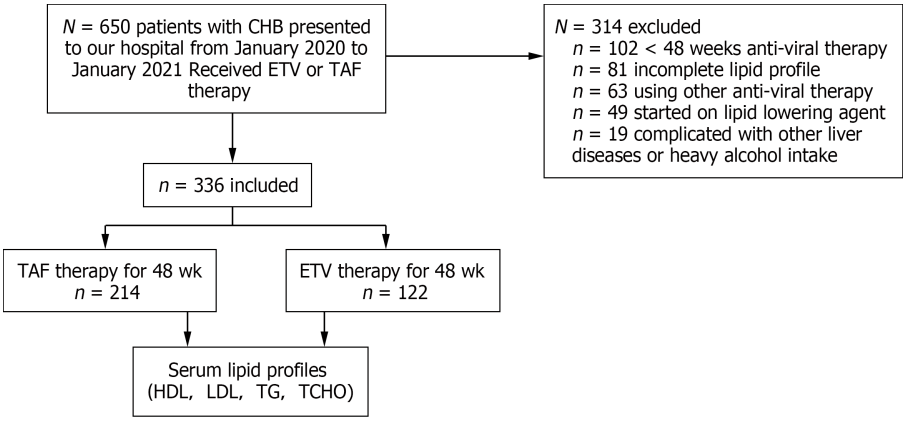

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Figure 1 Flowchart of study participants. CHB: Chronic hepatitis B; TAF: Tenofovir alafenamide; ETV: Entecavir; TCHO: Total cholesterol; HDL: High density lipoprotein; LDL: Low-density lipoprotein; TG: Triglycerides.

Risk factors were associated with elevated TCHO levels in CHB patients with 1-year TAF therapy

Logistic regression analysis was used to evaluate the risk factors associated with the worsening of TCHO levels (Figure 2). BMI, sex, hypertension, the baseline TCHO, and CK-MB levels were significantly associated with elevated TCHO levels. Furthermore, a nomogram incorporating statistically significant parameters in the logistic regression analysis was constructed, and the total points predicted the probability of elevated TCHO levels in individual patients.

DISCUSSION

In this real-life retrospective cohort study of 336 patients with CHB who received anti-viral therapy for 1 year, we compared fasting serum lipid profiles before and after initiation of either TAF or ETV treatment. In the TAF-treated cohort, we found a significant increase in the serum TCHO and TG levels compared with no difference in patients who received ETV. However, there were no concomitant significant changes in serum HDL or LDL levels in TAF-treated patients. Recent data have demonstrated that MetS increased the risk of progression of liver fibrosis independent of viral factors in patients with CHB[11,12]. Elevated TCHO and TG levels as MetS risk factors were related to a high risk of cirrhotic events in patients with CHB; thus, the results of this investigation may affect the decision regarding anti-viral therapy in CHB patients with cirrhotic risk factors.

TAF has been used as first-line therapy for CHB and HIV infections. Dyslipidemia and metabolic disorders have been linked to the prolonged use of TAF to treat HIV infection. Previous studies found that the serum lipid profile increased in HIV patients switching from TDF to TAF therapy, and the effect of increased serum lipids on the risk of cardiovascular events cannot be ignored[13-15]. Therefore, whether dyslipidemia due to TAF treatment in patients with CHB would lead to an increased risk of NAFLD is also a concern. Studies have reported that patients with CHB and NAFLD have better liver-related outcomes and overall mortality than those with CHB alone[16]. It is increasingly recognized that metabolic factors, which are precursors of NAFLD, can also be used to evaluate the risk of HCC in patients with CHB[17,18].

In our study, patients who received TAF therapy for 1 year did not have a significantly increased risk of developing NAFLD. However, owing to the short follow-up period of our study, the effect of TAF on increasing the incidence of NAFLD still needs to be evaluated over a longer follow-up period, and more data are required to better elucidate this.

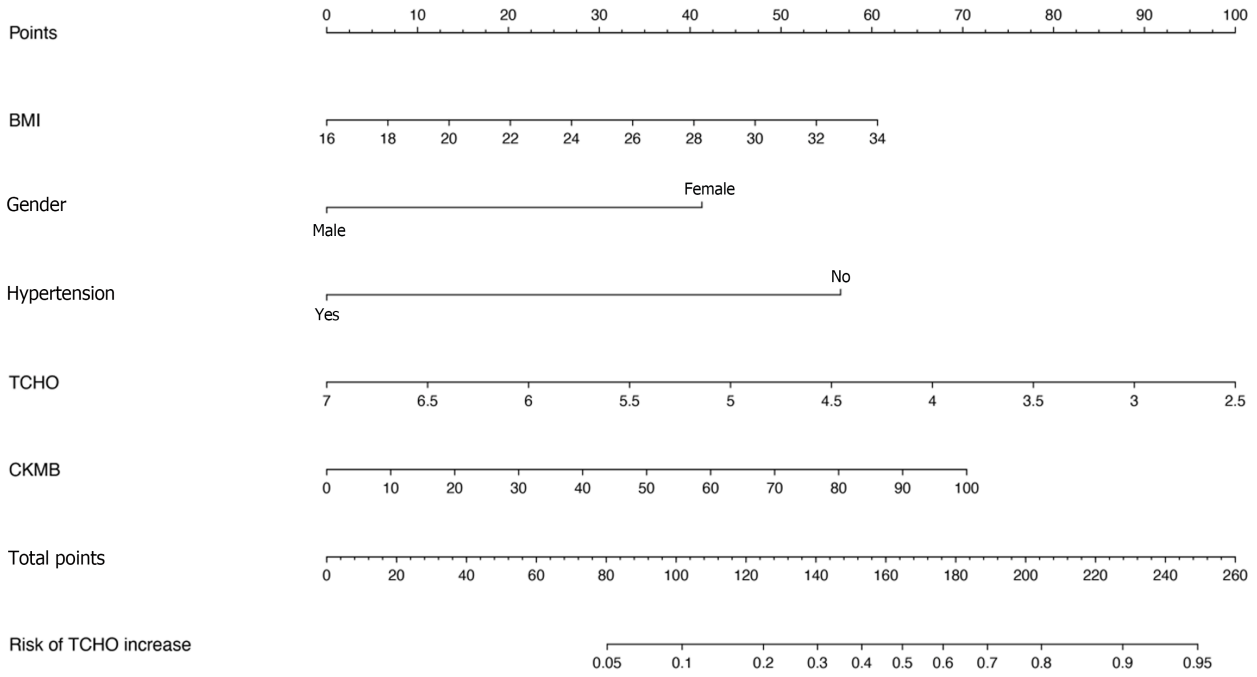

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Figure 2 Nomogram plot predicted the probability of the elevated total cholesterol level for individual patients receiving tenofovir alafenamide therapy. BMI: Body mass index; CK-MB: Creatine kinase-MB isoenzyme; TCHO: Total cholesterol.

It was unclear how TAF increased lipid concentrations, but the mechanism was independent of the patient's HIV status because a similar effect of TAF has been reported in HIV-negative patients receiving CHB therapy. Notably, a higher proportion of TAF-treated CHB patients experienced higher levels of LDL than the TDF group at the 48-wk follow-up[19,20]; however, the use of lipid-lowering agents was not described. In our study, the increased TCHO levels with TAF treatment represented a small change in the propensity score-matched model (5% higher than baseline, $P = 0.019$), but we did not find a significant change in the LDL profile compared to the ETV treatment group. Regular serum lipid measurements might not accurately capture the intricate alterations in lipid metabolism brought on by anti-viral medication. A recent study showed that TDF modulates lipid metabolism by upregulating hepatic CD36 *via* PPAR-a activation in patients with HBV infection[21]. However, the mechanism by which TAF increases serum lipid profiles remains unclear, and further studies are required.

In addition, in multivariate logistic regression analysis, metabolic factors, including BMI, hypertension, baseline TCHO, and CK-MB levels, were significantly associated with elevated TCHO levels, demonstrating an important impact of metabolic factors in terms of the elevated lipid profile caused by TAF. Previous studies have reported the effects of MetS on the adverse outcomes of fibrosis in patients with CHB[22,23]. Furthermore, some studies have confirmed that metabolic factors positively affected the risk of HCC in patients with HBV infection[17,24]. Based on the results mentioned above, the treatment options for patients with CHB who have the aforementioned aberrant metabolic variables may need to consider the potential effects of TAF medication on blood lipid levels.

Our study had some limitations. First, not all relevant clinical data were obtained from the treatment databases, and important data elements, such as lifestyle risk factors (*i.e.* exercise and diet) and family history, were not fully documented. Second, this was not a multicenter study, and we adjusted for baseline factors through a propensity score-matched model. Therefore, the observed increase in the TCHO profile may be due to the effect of anti-viral treatment. Third, the effect of TAF on the incidence of NAFLD cannot be elucidated well because of the short follow-up time. However, this study provided real-world data from China regarding the relationship between TAF-treated patients with CHB and changes in serum lipid levels. Large-scale multicenter prospective studies should be conducted in the future to further evaluate the effects of CHB and anti-HBV therapies on the risk of dyslipidemia, NAFLD, cirrhosis, and HCC.

CONCLUSION

In this real-life retrospective cohort study in China, we found that TAF was significantly associated with higher TCHO levels, whereas ETV had no effect in patients with CHB treated for 1 year. Risk factors (BMI, sex, baseline TCHO and CK-MB levels) were significantly associated with elevated TCHO levels. In the future, we will focus on increased NAFLD risk and not just changes in serum lipid profiles. Further studies will help elucidate the effect of TAF on long-term metabolic-related complications in patients with CHB.

ARTICLE HIGHLIGHTS

Research background

In recent decades, the prevalence of nonalcoholic fatty liver disease (NAFLD) has significantly increased in China, leading to the coexistence of NAFLD and chronic hepatitis B (CHB). Many patients require long-term anti-hepatitis B virus (HBV) therapy with potent oral drugs tenofovir alafenamide (TAF) and entecavir (ETV), which are recommended as first-line treatment in HBV clinical practice guidelines. However, no studies have compared the effects of TAF and ETV on lipid profiles in HBV-treated patients. Meanwhile, there are limited data on the effects of TAF on metabolism-related complications in real-world settings.

Research motivation

Many patients require long-term anti-HBV therapy with the potent oral drugs TAF and ETV, which are recommended as first-line treatment in HBV clinical practice guidelines. TAF has a serum lipid-raising effect in patients with HIV; however, its effect on serum lipids and NAFLD risk in patients with CHB is unclear.

Research objectives

This retrospective cohort study aimed to characterize the effect of TAF on serum lipid levels and NAFLD risk in patients with CHB, and we compared the pretreatment and post-treatment serum lipid profile changes after initiation of either TAF or ETV anti-viral therapy.

Research methods

The data including the clinical features, serum lipids, and metabolic factors of patients with CHB at baseline and approximately 1 year after TAF or ETV treatment were collected and analyzed. We used propensity score-matched models to assess the effects on high-density lipoprotein, low-density lipoprotein, triglycerides, and total cholesterol (TCHO).

Research results

Compared with the ETV group, the TAF group had significantly higher TCHO levels after treatment (4.67 ± 0.90 *vs* 4.36 ± 1.05, P=0.006). In a propensity score-matched model, TAF-treated patients had significantly increased TCHO levels compared to that at baseline (P = 0.019), while there was no difference for the ETV group. Body mass index, sex, hypertension, baseline TCHO, and creatine kinase-MB isoenzyme levels were significantly associated with elevated TCHO levels in logistic regression analysis. However, 1-year TAF treatment did not increase the incidence of NAFLD.

Research conclusions

Our study found that a greater increase in TCHO was observed in patients with CHB receiving TAF than in those receiving ETV; however, TAF-induced dyslipidemia did not increase the incidence of NAFLD.

Research perspectives

This was not a multicenter study, and most of patients with CHB in this study were Asians. Large-scale multicenter prospective studies should be conducted in the future to further evaluate the effects of CHB and anti-HBV therapies on the risk of dyslipidemia, NAFLD, cirrhosis, and hepatocellular carcinoma.

FOOTNOTES

Author contributions: Lai RM and Lin S contributed equally to this work; Lai RM and Lin S conceived and designed the study; Chen TB and Zhou JH contributed to the data analysis and manuscript feedback; Li N and Wang MM collected clinical data of the patients; Lai RM and Zheng Q wrote the manuscript; All authors approved the final version of the manuscript.

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Institutional review board statement: This retrospective study was approved by the ethics committee at the First Affiliated Hospital of Fujian Medical University, China.

Informed consent statement: Patients were not required to give informed consent to the study as the analysis used anonymous data that were obtained after each patient agreed to treatment by written consent.

Conflict-of-interest statement: All the authors declare that they have no conflicts of interest related to the manuscript.

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STROBE statement: The authors have read the STROBE Statement – checklist of items, and the manuscript was prepared and revised according to the STROBE Statement – checklist of items.

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ORCID number: Rui-Min Lai 0000-0003-2911-0273; Tian-Bin Chen 0000-0002-9136-2167; Yue-Yong Zhu 0000-0002-0746-4911; Qi Zheng 0000-0001-8006-7069.

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