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Retrospective Study

Improvement of Hepatic Fibrosis after Tenofovir Disoproxil Fumarate Switching to Tenofovir Alafenamide for Three Years

TDF Switching to TAF Improve Hepatic Fibrosis

Tung Huynh, Delana MyAn Bui, Tina Xiwen Zhou, Ke-Qin Hu

Abstract

BACKGROUND

Both tenofovir Alafenamide (TAF) and Tenofovir Disoproxil Fumarate (TDF) are the first-line treatments for chronic hepatitis B (CHB). We have showed switching from TDF to TAF for 96 weeks resulted further ALT improvement, but data remain lacking on the long-term benefits of TDF switching to TAF on hepatic fibrosis.

AIM

To assess the benefits of TDF switching to TAF for 3 years on ALT, AST, and hepatic fibrosis improvement in CHB patients.

METHODS

A single center retrospective study on 53 patients with CHB who were initially treated with TDF, then switched to TAF to determine dynamic patterns of ALT, AST, APRI, FIB-4 scores, and SWE improvement at week 144, and the associated factors.

RESULTS

Mean age 55 (28-80) ; 45. 3%, males; 15. 1%, clinical cirrhosis; mean baseline ALT, 24. 8; AST, 25. 7 IU/L; APRI, 0. 37; and FIB-4, 1. 66. After 144 weeks TDF switching to TAF, mean ALT and AST were reduced to 19. 7 and 21, respectively; and rates of ALT and AST < 35 (male) /25 (female) and < 30 (male) /19 (female) were persistently increased from baseline to week-144. Hepatic fibrosis was also improved from baseline to week-144 by APRI < 0. 5, from 79. 2% to 96. 2%; FIB-4 < 1. 45, from 52. 8% to 58. 5%; mean APRI was reduced to 0. 27 and FIB-4 to 1. 38; and mean SWE reading from 7. 05 to 6. 30 kPa. Renal function was stable and rate of patients with GFR > 60 mL/min was increased from 86. 5% to 88. 2%.

CONCLUSION

Our data confirmed that switching from TDF to TAF for 3 years results in not only persistent ALT/AST improvement, but also hepatic fibrosis improvement by APRI, FIB-4 scores, as well as SWE reading, the important clinical benefits of long-term HBV antiviral treatment with TAF.

Key Words: Tenofovir alafenamide (TAF) ; Tenofovir disoproxil fumarate (TDF) ; Switching; Hepatic fibrosis improvement; APRI; FIB-4; Shear wave elastography

Core Tip: Both tenofovir disoproxil fumarate (TDF), entecavir (ETV), and tenofovir alafenamide (TAF) have been used as first-line therapy for chronic hepatitis B. In this study, we assessed the effect of TDF switching to TAF for 3 years (144 weeks) on dynamic changes of ALT, AST, APRI, FIB-4 scores and shear wave elastography. Our study demonstrated that switching from TDF to TAF for 3 years results in persistent mean ALT and AST reduction with high rate of normalization, and also hepatic fibrosis improvement assessed by mean APRI and FIB-4 scores, as well as SWE reading reduction and great improvement rates.

INTRODUCTION

Hepatitis B virus (HBV) infection is a major global health concern that involves the risk of cirrhosis and hepatocellular carcinoma (HCC). World Health Organization (WHO) estimates that approximately 296 million people were living with chronic HBV infection in 2019, with approximately 1. 5 million people become newly infected each year. In 2019, chronic hepatitis B (CHB) resulted in an estimated 820, 000 deaths, mostly from cirrhosis and HCC[1]. Antiviral therapy with nucleos (t) ide analogues (NAs) is currently the main treatment option that has significantly improved the outcomes in patients with CHB. The NAs, tenofovir disoproxil fumarate (TDF), approved in 2008, and entecavir (ETV), approved in 2005, have been recommended by international guidelines and used as first-line therapy for CHB. Prolonged treatment with these NAs has been associated with reduction in progression to cirrhosis, lower risk of HCC, and reversal of hepatic

decompensation by sustained suppression of HBV DNA[2-4]. Tenofovir alafenamide (TAF), approved in 2016, provided another treatment option for patients with CHB. TAF is a prodrug of tenofovir with greater plasma stability, allowing for more efficient uptake by hepatocytes with less peripheral drug exposure of metabolites, tenofovir diphosphate, reaching the kidney compared to TDF, thus, better safety profile, also becomes one of the first line option for HBV treatment[5, 6].

Stage of liver fibrosis is very important to determine severity and prognosis, and prioritize for treatment in CHB patients. Previously, the only method of staging the degree of fibrosis was liver biopsy, which has been the gold standard for evaluation of liver fibrosis[7]. In addition to staging fibrosis, it can grade steatosis, necrosis, and inflammatory activities; however, there are limitations of this procedure including cost, risk of serious complications, sampling errors, and observer technical differences[8]. Various non-invasive methods ranging from serum markers to imaging techniques have been developed over the past decade to stage liver fibrosis. Several scoring systems such as aspartate aminotransferase (AST) to platelet ratio index (APRI) and fibrosis index based on four factors (Fibrosis-4 index, FIB-4) have been widely validated in large cohort studies[9, 10]. Imaging is another option to stage liver fibrosis noninvasively, including transient elastography (TE) and shear wave elastography (SWE) [11, 12].

Prior studies have demonstrated the benefits of switching from TDF to TAF including better renal profile and bone safety[13-16]. Previously, we have showed switching from TDF to TAF treatment for 96 weeks resulted in further ALT improvement, but data remain lacking on its long-term effect on biochemical changes and hepatic fibrosis[17]. The present study assessed the effect of TDF switching to TAF for 3 years (144 weeks) on dynamic changes of ALT, AST, APRI, FIB-4 scores and SWE, and the associated factors.

MATERIALS AND METHODS

Study design and patient enrollment

This was a single-center retrospective study. Institutional Review Board (IRB) approval was obtained, and informed consent was waived. Patients with CHB who were initially treated with TDF, then switched to TAF in the Liver Clinic at UCI Medical Center were assessed and enrolled if they met the inclusion criteria. Inclusion criteria included patients who had CHB and ruled out other chronic liver diseases were treated with TDF then completed the switching to TAF and had regular follow-up at week 144. Exclusion criteria included patients with treatment course less than 144 weeks or missing lab data during the switching treatment and follow-up.

Of the 60 charts of patients reviewed from 12/2016 to 09/2021, 7 patients were excluded from the study due to missing lab data during the switching, or lack of 144 weeks post switching follow-up. Consequently, 53 patients met the inclusion criteria and were included in the present study.

Data collection

Baseline data collection included age, gender, ethnicity, body mass index (BMI), diagnosis of cirrhosis, spleen size, HBV genotype, and presence of HBeAg. The diagnosis of clinical cirrhosis was made based on radiographic, histologic findings, or endoscopic finding of esophageal/gastric varices. Radiographic findings included presence of nodular liver, splenomegaly (> 12 cm), and /or ascites. Histologic findings included presence of stage 3-4 fibrosis. Baseline and follow-up lab data included levels of creatinine, complete blood count (white blood cells, hemoglobin, and platelets), alanine aminotransferase (ALT), aspartate aminotransferase (AST) were collected at the time points of switching and at week 24, 48, 96, and 144. ALT and AST were quantified using UV/NADH-Rate method with reference range 7 - 40 IU/L on the Beckman Coulter AU analyzer. Both AST to platelet ratio index (APRI) and Fibrosis-4 (FIB-4) scores were calculated at baseline and at week 144. Shear wave elastography (SWE) was performed at baseline and at time point after TAF switching.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Science software (SPSS, version 25, Chicago, IL). Categorical variables were reported as numbers and percentages or means with ranges. Data values were compared using Pearson Chi-square ($\chi 2$) test. The analysis of variance (ANOVA) was used to compare means. Both univariate and multivariate analyses were performed to evaluate the association between different variables of biochemical and clinical response during the switching time points and ALT/AST, APRI, FIB-4, and SWE improvement. All tests for significance were two-tailed and $P < 0.05$ was considered statistically significant.

RESULTS

Pre-switching demographics, laboratory values, and APRI and FIB-4 scores

The demographic characteristics of the study population are summarized in Table 1. The mean age of the cohort was 55 (28 - 80) years; 35 (66%) patients, age > 50 year-old; 24 (45. 3%) patients were male. Among the 53 patients, 51 (96. 2%), 1 (1. 9%), and 1 (1. 9%) were Asian, Hispanic, and other races, respectively. Seventeen (32. 1%) patients had BMI ≥ 25 kg/m^2. Clinical cirrhosis was diagnosed in 8 (15. 1%) patients. Four (7. 7%) patients had spleen size > 12 cm. In 24 patients with identified HBV genotype, 2 (8. 3%) patients had genotype A; 15 (62. 5%), genotype B; 6 (25%), genotype C; and 1 (4. 2 %), genotype D. Fifteen (28. 3%) patients were HBeAg-positive.

Baseline laboratory variables were shown in Table 1. Mean serum ALT was 24. 8 (7 - 108) IU/L; mean serum AST, 25. 7 (15 - 89) IU/L; mean APRI score, 0. 37 (0. 13 – 0. 92) ; and mean FIB-4 score, 1. 66 (0. 49 – 5. 33). In 53 patients, 79. 2% had APRI < 0. 5; 52. 8%, FIB-4 < 1. 45. Six of 53 (11. 3%) patients had platelets ≤ 120 x 10^9/L. At baseline, 73. 6% of patients had ALT < 35 (males) /25 (female) IU/L (35/25) ; 77. 4%, AST < 35/25; 67. 9%, both ALT/AST < 35/25; 54. 7%, ALT < 30 (males) /19 (female) IU/L (30/19) ; 47. 2%, AST < 30/19; and 39. 6%, both ALT/AST < 30/19. Mean serum creatinine was 0. 86 (0. 5 - 1. 7) mg/dL, and 86. 5% of patients had glomerular filtration rate (GFR) > 60 mL/min.

Dynamic changes in ALT, AST after switching for 144 weeks and variables associated with their improvement

Our previous study and other studies have showed the improvement of ALT at post-switching week 96[17, 18]. In the present study, we further assessed the biochemical changes after switching to beyond 96 weeks. In our study cohort, both ALT and AST normalization and the improvement rates were persistent after switching for 96 weeks and up to 144 weeks. As shown in Figure 1, the means (ranges) of ALT and AST were all improved persistently after switching. The mean ALT was reduced to 20. 8 (8-106), 19. 1 (7-40), 19. 5 (9-42), and 19. 7 (8-42), P < 0. 001; mean AST was reduced to 21. 4 (13-59), 20. 3 (14-38), 21. 2 (13-41), and 21 (13-39), P < 0. 001, at switching week 24, 48, 96, and 144, respectively. As shown in Figure 2A, the improvement rates to ALT < 35/25 was increased from 73. 6% to 84. 9%; AST < 35/25, from 77. 4% to 92. 5%; and both ALT/AST < 35/25, from 67. 9% to 83% at baseline to switching week 144, respectively. Additionally, as shown in Figure 2A, the improvement rates to ALT < 30/19 was increased from 54. 7% to 66%; AST < 30/19, from 47. 2% to 58. 5%; and both ALT/AST < 30/19, from 39. 6% to 54. 7% at baseline to switching week 144, respectively.

We then assessed different variables associated with ALT/AST improvement. As shown in Table 2, univariate analysis showed that improvement of the ALT to < 30/19 at week 144 was significantly associated with male gender (P = 0. 016), ALT < 30/19 (P = 0. 024), APRI < 0. 5 (P = 0. 027), and ALT < 35/25 at treatment (Rx) week 24 (P = 0. 008), but not with age > 50 year-old (P = 0. 945), BMI > 25 kg/m^2 (P = 0. 888), clinical cirrhosis (P = 0. 299), pre-Rx spleen size > 12 cm (*P* = 0. 442), platelet < 120 x 10^9/L (P = 0. 078), AST < 30/19 (P = 0. 123), FIB-4 < 1. 45 (P = 0. 399), and AST < 35/25 at Rx week 24 (P = 0. 071).

Dynamic changes in APRI, and FIB-4 score after switching at week 144 and variables associated with their improvement

After TDF switching to TAF, the means (ranges) of APRI, and FIB-4 were all improved persistently. The mean APRI was reduced from 0. 37 (0. 13-0. 92) to 0. 27 (0. 11-0. 51), P

< 0. 001 (Figure 3A) ; the mean FIB-4, from 1. 66 (0. 49-5. 33) to 1. 38 (0. 39-2. 76), P < 0. 001 (Figure 3B) at switching week 144. The rate of APRI score improvement to < 0. 5 was increased from 79. 2% at baseline to 96. 2%, and the rate of FIB-4 score improvement to < 1. 45, from 52. 8% at baseline to 58. 5% at switching week 144 (Figure 2B).

Having demonstrated the significant improvement of APRI and FIB-4 scores, we then assessed different variables associated with the improvement. As shown in Table 2, univariate analysis showed that APRI improvement to < 0. 5 at switching week 144 was significantly associated with absence of clinical cirrhosis (P = 0. 001), pre-Rx spleen size < 12 cm (P = 0. 001) and platelet 120 x 10^9/L (P = 0. 001), APRI < 0. 5 (P = 0. 001) and AST < 35/25 at week Rx 24 (*P* = 0. 021), but not with the male gender (P = 0. 891), age > 50 year-old (P = 0. 625), BMI > 25 kg/m^2 (P = 0. 58), ALT < 30/19 (P = 0. 534), AST < 30/19 (P = 0. 054), ALT < 35/25 (P = 0. 16), and FIB-4 < 1. 45 at Rx week 24 (P = 0. 156). FIB-4 improvement to < 1. 45 at post-Rx week 144 was significantly associated with age > 50 year-old (P = 0. 001), BMI > 25 kg/m^2 (P = 0. 001), absence of clinical cirrhosis (P = 0. 037), and FIB-4 < 1. 45 at week Rx 24 (P = 0. 001), but not with male gender (P = 0. 272), pre-Rx spleen size > 12 cm (P = 0. 142) and platelet < 120 x 10^9/L, (P = 0. 221), ALT < 30/19 (P = 0. 319), AST < 30/19 (P = 0. 07), ALT < 35/25 (P = 0. 304), AST < 35/25 (P = 0. 486) or APRI < 0. 5 at Rx week 24 (P = 0. 106).

Changes in SWE measurement after switching at week 144

We then assessed the improvement of liver fibrosis after TDF switching to TAF by SWE reading. In our study, the reference values of SWE were fibrosis stage 0-1, if the reading < 7. 1 kPa; stage 2, if the reading ≥ 7. 1 and < 8. 7 kPa; stage 3, if the reading ≥ 8. 7 and < 10. 4 kPa; and stage 4, if the reading ≥ 10. 4 kPa[19-21]. In 42 cases with follow-up SWE, the overall improvement of liver fibrosis by SWE reading and fibrosis stages was 95% and the mean SWE reading was improved from 7. 05 to 6. 30 kPa after a mean of 109 weeks (range 21 – 196) switching (Figure 3C). Compared to baseline SWE reading, the improvement rate to fibrosis stage 0-1 was increased from 64% to 86%. The stage 2

fibrosis cases were reduced from 16% to 4%, stage 3 fibrosis cases were reduced from 8% to 2%, and stage 4 fibrosis cases were reduced from 12% to 8% at Rx week 144, respectively. Overall, 95. 3% had fibrosis improvement at switching Rx week 144.

Renal function benefits after switching at week 144

Previous studies have showed switching from TDF to TAF results in improvement of renal function[13, 14]. In our study, the mean serum creatinine was stable at 0. 88 (0. 5-1. 8) mg/dL from baseline to switching Rx week 144, and the rate of GFR > 60 mL/min was improved from 86. 5% at baseline to 88. 2% at switching Rx week 144 (P < 0. 001).

DISCUSSION

To our knowledge, few real-world studies have thus far reported the benefits of switching from TDF to TAF for up to week 96[17, 18], but there is limited data on long-term benefit of this switching to beyond 96 weeks, including fibrosis improvement. Our study evaluated the clinical benefits after 144 weeks of TDF switching to TAF by assessing the changes in biochemical markers ALT and AST, non-invasive fibrosis score APRI and FIB-4, and liver stiffness measurement (LSM) with SWE.

ALT normalization under antiviral treatment has been associated with a decrease in viral replication, tissue damage and necroinflammation. Our previous and other studies showed that switching from TDF to TAF resulted in high rates of ALT and AST improvement at switching week 96[17, 18]. A significant reduction of liver enzymes was observed after switching from TDF to TAF for 6 months[22], and improvement in ALT normalization with ALT level < 35 (IU/L) for men and < 25 (IU/L) for women up to 96 weeks post-switching[23]. The present study further assessed the benefit of switching from TDF to TAF for 144 weeks. We demonstrated that the mean ALT was further reduced from 24. 8 to 19. 6 and 19. 7 IU/L, and the mean AST was also reduced from 25. 7 to 21. 2 and 21 IU/L from baseline to week 96 and 144 week switching, respectively. Our study showed further persistent improvement rate of ALT, AST, and both

ALT/AST to < 35/25 from baseline to post-switching week 144. Our results were not only consistent with Toyoda *et al*[21] study which showed great improvement of ALT/AST < 35/25 at switching week 96, but also demonstrated further persistent improvement from week 96 to week 144 after the switching. In addition, in the present study, we assessed the improvement rate of biochemical criteria ALT/AST to < 30/19. The improvement rates of ALT, AST, and both ALT/AST to < 30/19 were persistently increased from baseline to post-switching week 144. Our data not only confirmed the benefit of ALT and AST improvement after TDF to TAF switching for two years, but also demonstrated the additional benefit that by ALT/AST to < 35/25 and < 30/19 criteria, prolonged treatment course from TDF switching to TAF for 3 years could result in 21% reduction in mean ALT and 18% reduction in mean AST, and improved rates of both ALT and AST normalization.

Our study showed that the improvement level to < 30 (IU/L) for men and < 19 (IU/L) for women of ALT and AST at switching week 144 was significantly associated with male gender, ALT < 30/19 and < 35/25, APRI < 0. 5 at week 24, but not age, BMI, cirrhosis, pre-Rx spleen size > 12 cm, platelet < 120 x 10^9/L, AST < 30/19, and < 35/25 at week 24. Our real world data confirmed results from clinical trials which show TAF ensues continued increase in not only viral suppression, but also ALT and AST normalization[14, 16], a unique benefit of long-term TAF treatment.

Besides ALT/AST normalization, another goal of HBV treatment is to slow down the progression of liver fibrosis and even to achieve resolution of liver fibrosis[24, 25]. Our previous study showed that HCV direct acting antiviral treatment resulted in highly durable improvement rates of ALT and AST, APRI and FIB-4 scores in HCV patients[26]. Liu *et al*[27] reported a significant decrease of both APRI and FIB-4 after 5 years of treatment with ETV in 303 HBeAg-negative CHB patients. There were limited studies on the effect of switching TDF to TAF on the improvement of APRI and FIB-4 scores. Our study demonstrated the mean APRI was significantly reduced from 0. 37 to 0. 27 and the improvement rate of APRI to < 0. 5 was increased from 79. 2% to 96. 2%, equal to 27% reduction in mean APRI and 1. 2-times improvement rate of APRI to < 0. 5.

Likewise, we also found that the mean FIB-4 score was significantly reduced from 1. 66 to 1. 38 and the improvement rate of FIB-4 to < 1. 45 was increased from 52. 8% to 58. 5%, equal to 16. 9% reduction in mean FIB-4, and 1. 1-times improvement rate of FIB-4 to < 1. 45 after the switching to TAF for 144 weeks. Univariate analysis showed that the improvement of APRI to < 0. 5 and FIB-4 to < 1. 45 was both significantly associated with absence of clinical cirrhosis. Our study demonstrated switching from TDF to TAF for 144 weeks resulted in hepatic fibrosis regression in CHB patients with persistent improvement in APRI and FIB-4, another important benefit of such treatment switch. Additionally, our data provided supportive evidence of clinical application of both APRI and FIB-4 scores in assessing the effectiveness of antiviral in HBV treatment.

LSM, including TE and SWE, has become a standard clinical practice for liver fibrosis assessment. To further determine the long-term clinical benefit of TDF switching to TAF in liver fibrosis improvement as indicated by APRI and FIB-4 scores, we assessed if 144 weeks switching could also impact SWE reading. We found that after switching from TDF to TAF for a mean of 109 weeks, the mean SWE reading was improved from 7. 05 to 6. 30 kPa, equal to 10. 6% score improvement, and the fibrosis stage 0-1 was increased from 64% to 86%, equal to 34. 4% improvement. Together with APRI and FIB-4 scores improvement, the above SWE results further confirmed clinical benefits and superiority in liver fibrosis improvement after switching from TDF to TAF for 144 weeks. These benefits might be due to TAF has greater stability in plasma than TDF and allows more efficient uptake by hepatocytes and higher circulating intra-hepatocytic concentration of active metabolites allowing more prominent liver targeting ability[5, 6]. In addition, TAF enters hepatocytes by passive diffusion and efficiently taken up by hepatocytes and then hydrolyze to form tenofovir which undergoes phosphorylation to active metabolite, tenofovir diphosphate. Compared to TDF, TAF provides more persistent intracellular level of tenofovir diphosphate, a potent inhibitor of HBV replication[28, 29] and results in more reduced hepatic inflammation and liver fibrosis.

In the present study, our results also showed the renal benefits of switching from TDF to TAF. After 144 weeks of switching, the renal function was stable and even further

improved as indicated by stable mean serum creatinine and increased rate of GFR > 60 mL/min from 86. 5% at baseline to 88. 2%. Our data was consistent with previous studies on the renal benefits of TAF switching[13, 14].

Some limitations should be noted in our study. First, this was a single-center retrospective study with small sample size, especially the patients with advanced liver fibrosis. Secondly, we did not have follow-up liver biopsy data to reference the non-invasive fibrosis test results. However, it is the first study to further assess the long-term benefits of switching TDF to TAF on biochemical changes of ALT, AST, APRI, FIB-4, and SWE scores. Future studies with larger sample size are warranted to confirm our findings.

CONCLUSION

In summary, the present study demonstrated that switching from TDF to TAF for 3 years results in not only persistent ALT and AST improvement, but also hepatic fibrosis improvement assessed by APRI and FIB-4 scores, as well as SWE reading, the important clinical benefits of long-term HBV antiviral treatment with TAF.

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