Renal Safety of Tenofovir Alafenamide versus Tenofovir Disoproxil Fumarate for the Treatment of Chronic Hepatitis B Patients: An Evidence-based Case Report

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ABSTRACT

Background: *Treatment modalities for chronic hepatitis B infection (CHB) are interferon and antiviral. The most commonly used antiviral is tenofovir disoproxil fumarate (TDF). However, it has nephrotoxic effects. Recently, a new antiviral tenofovir alafenamide (TAF), which also inhibits the hepatitis B virus (HBV), has been developed. This study aimed to compare the renal safety of TAF and TDF.*

Method: *Literature searching was conducted in PubMed/Medline and Cochrane databases, with modified keywords as "chronic hepatitis B", "tenofovir alafenamide", "tenofovir disoproxil fumarate", "renal" with BOOLEAN logic. The articles obtained will be selected and carried out for critical appraisal of validity, importance, and applicability.*

Results: *Four double-blind, randomized clinical trials (RCT) studies were obtained for analysis. The antiviral effects of TAF and TDF groups were not significantly different. The increase in serum creatinine of the TAF group was significantly smaller than that of the TDF group in three studies ($p < 0.05$). In contrast, one study showed no significant difference ($p = 0.32$). The decrease in eGFR (estimated-Glomerular Filtration Rate) in the TAF subjects was smaller than TDF in three studies ($p <0.001$), whereas one study found an increase in eGFR in the TAF subjects ($p = 0.00034$). There were no severe side effects found in both study groups.*

Conclusion: *Based on the scientific evidence, TAF is safer for the renal than TDF. However, the antiviral effect is not significantly different.*

Keywords: chronic hepatitis B, tenofovir alafenamide, tenofovir disoproxil fumarate, renal function

ABSTRAK

Latar Belakang: Modalitas pengobatan untuk infeksi hepatitis B kronis adalah interferon dan antivirus. Antivirus yang paling umum digunakan adalah tenofovir disoproxil fumarate (TDF), namun diketahui memiliki nefrotoksisitas. Belakangan ini, tenofovir alafenamide (TAF) antivirus baru telah dikembangkan, yang juga menghambat virus hepatitis B. Penelitian ini bertujuan untuk membandingkan keamanan ginjal dari TAF dan TDF.

Metode: Pencarian artikel dilakukan di database Pubmed/Medline dan Cochrane, dengan kata kunci yang dimodifikasi seperti "hepatitis B kronis", "tenofovir alafenamide", "tenofovir disoproxil fumarate", "renal" dengan logika BOOLEAN. Artikel yang diperoleh akan diseleksi dan dilakukan telaah kritis mengenai validitas, importance, dan applicability.

Hasil: Empat studi double-blind randomized-clinical trials (RCT) diperoleh untuk analisis. Efek antivirus kelompok TAF dan TDF tidak berbeda nyata. Peningkatan serum kreatinin kelompok TAF secara signifikan lebih kecil dibandingkan kelompok TDF dalam tiga studi (p <0,05). Sedangkan satu penelitian menunjukkan tidak berbeda signifikan (p = 0,32). Penurunan eGFR (estimated-Glomerular Filtration Rate) pada subjek TAF lebih kecil dari TDF pada tiga penelitian (p<0,001), sedangkan satu penelitian menemukan peningkatan eGFR pada subjek TAF (p=0,00034). Tidak ada efek samping parah yang ditemukan pada kedua kelompok studi.

Simpulan: Berdasarkan bukti ilmiah yang diperoleh, TAF lebih aman untuk ginjal daripada TDF. Walaupun efek antivirusnya tidak jauh berbeda.

Kata kunci: hepatitis B kronis, tenofovir alafenamide, tenofovir disoproxil fumarate, fungsi ginjal

INTRODUCTION

Chronic hepatitis B infection (CHB) is a world medical condition that is assessed to influence 257-291 million individuals internationally. In 2015, almost 887,000 deaths were caused by HBV infection. CHB can develop into conditions such as chronic liver disease, liver cirrhosis, and liver cancer.[1] Based on WHO data in 2019, 6.6 million people with hepatitis B received therapy.[2] Patients with CHB who do not receive adequate treatment may increase their risk of liver cirrhosis, hepatocellular carcinoma (HCC), and liver decompensation3 in 15% to 40% of them.[3]

Over the decades, chronic hepatitis B therapy has progressed. This therapy aims to slow the progression of CHB to cirrhosis of the liver and reduce the incidence of liver cancer. One of the most widely used antivirals is tenofovir disoproxil fumarate (TDF). Treatment with TDF can suppress viral progression in approximately 90% of patients and slow progression to cirrhosis hepatis.[3,4] However, several studies have shown that TDF is closely related to decreased kidney function. TDF is known to have nephrotoxicity effects and decrease bone density in long-term and short-term use.

Nephrotoxicity is seen in roughly 15% of patients treated with TDF for 2-9 years. Normal observing of the renal capability to decide creatinine clearance (CrCl) is significant during TDF administration.[5,6] As of late, a novel prodrug of tenofovir-diphosphate has been created, tenofovir alafenamide (TAF), a nucleotide that restrains HBV and HIV-1 records. TAF showed better antiviral movement at lower dosages and was more steady intracellularly and extracellularly. Tenofovir will be converted to its active form, namely tenofovir diphosphate, which is 90% lower in plasma than TDF. Thus, lower systemic drug exposure, including nephrons, can reduce the effect of TAF on renal toxicity.[7]

CLINICAL QUESTION

A 27-year-old woman was diagnosed with CHB. The analysis of hepatitis B in this understanding was made involving the symptomatic rules of the American Association for The Study of Liver Disease (AASLD) 2007.[8] The diagnosis of hepatitis B meets the following criteria: HBsAg positive > a half year, HBV DNA > 20,000 IU/mL (lower upsides of 2,000-20,000 IU/mL can be found in HBeAg negative), tenacious or irregular raised ALT, liver biopsy showing hepatitis ongoing with moderate to extreme level of necroinflammation.

This patient was known to be HBsAg reactive in June 2020 and returned with complaints of yellow eyes, weakness, fatigue, joint pain, and headache in March 2021. Liver function examinations in January 2021 and March 2021 found a persistent increase in ALT. The patient was tested for HBsAg and found to be reactive. The patient then performed an independent

HBV DNA RT-PCR examination and found 1.17 x 105 IU/mL. The patient was then prescribed Tenofovir Disoproxil Fumarate (TDF) 300 mg/day, and an IEC was performed that could cause impaired kidney function.

The patient then asked for a choice of other drugs that did not cause impaired kidney function but at a price that was not too expensive. Doctors know alternative drug choices according to patient criteria, namely Tenofovir Alafenamide (TAF). To determine the safety of TAF drugs on the kidneys, the doctor took several EBCR steps, including formulating questions, seeking scientific evidence, conducting critical appraisals, answering questions, and assessing outcomes. Based on the case illustration, the clinical question can be formulated: "Is TAF safer than TDF for kidney function in Chronic Hepatitis B patients?"

Table 1. Formulation of clinical questions based on PICO

Population	Patients with Chronic Hepatitis B
Intervention	Tenofovir Alafenamid (TAF)
Comparison	Tenofovir Disoproxil Fumarate (TDF)
Outcome	Renal Funcion

METHOD

Literature searching was done in PubMed/Medline and Cochrane databases using the following keywords, "chronic hepatitis B" OR "CHB" AND "tenofovir alafenamide" OR "TAF" AND "tenofovir disoproxil fumarate" OR "TDF" AND "renal". The consideration models included a clinical preliminary review plan, English language, and human exploration subjects. The avoidance standards were research subjects other than the substance of this paper, like liver cirrhosis and acute Hepatitis B infection. After the data search was carried out, we found 12 articles. Of these 12 articles, all are written in English, and only 10 can be accessed in full text, while 2 cannot be accessed in full text. So, in the next search stage, only 10 articles will proceed to the next article selection stage.

The next stage of selection is to read the entire 10 articles. The article used is a Randomized Clinical Trials (RCT) study comparing CHB therapy with TAF and TDF. At this stage, 6 articles were excluded because they did not clearly compare TAF with TDF, were review articles, and discussed CHB therapy in general.

Thus, in preparing this EBCR, 4 RCT studies were included in the inclusion criteria. These 4 articles will then be subjected to a critical appraisal of RCT studies using articles written by Buti et al., Chan et al., Agarwal et al., and Lampertico et al., the articles will then be assessed for validity, importance, and applicability in this EBCR.

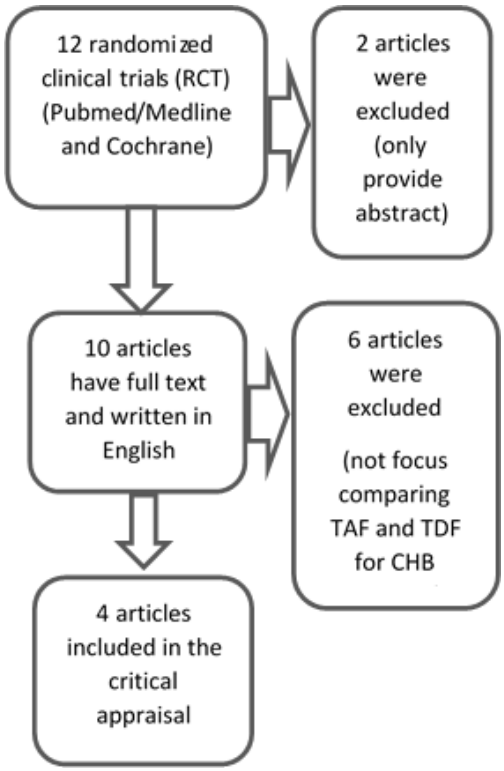

Figure 1. Flowchart of the selected articles used in the EBCR

RESULTS

Based on the results of the selection of articles, 4 studies were suitable for further analysis in our evidence-based case report. The study consisted of four double-blind, randomized clinical trials. The results of the critical appraisal of these four studies are described in Table 2-5. This RCT study aims to determine the efficacy and safety of TAF or TDF in patients with chronic hepatitis B. This study was obtained from the Pubmed/Medline and Cochrane databases published in the last 5 years.

Critical Appraisal

This evidence-based case report of 4 RCT studies uses guidelines from the University of Oxford's Center for Evidence-Based Medicine (CEBM). The critical appraisal form described includes three aspects: validity, importance, and applicability. We separate the critical appraisal results into several tables, where

validity is discussed in Table 2 and 3, importance is discussed in Table 4, and applicability is discussed in Table 5. We conclude that all four RCT studies are valid, important, and relevant to our patients according to the level of evidence 1b.

A recent study by Buti et al. described HBeAg negative patients as randomized 2:1 in the phase 3 study. CHB patients in the 2 groups were given 25 mg TAF or 300 mg TDF in a double-blind manner. This is related to the objective of the outcome of the therapy. From the analysis of 425 patients found non-inferiority of TAF to TDF. This is indicated by the achievement of plasma HBV DNA concentrations <29 IU/mL at week 48, with a percentage difference at baseline of 1.8% (-3.6% to 7.2%) with 95% CI.[3]

Statistically, the percentage of CHB patients who achieved HBV DNA levels <29 IU/mL between two treatments in all subjects evaluated was not different. The patients in this RCT were no less than 18 years old. They had HBV DNA levels >20,000 IU/mL, serum alanine aminotransferase (ALT) >60 IU/L in men and >38 U/L in ladies, with an expected CrCl of 50 mL/minute in view of estimations utilizing the Cockcroft-Gault technique. Following 48 weeks, TAF and TDF organization showed a negligible expansion in serum creatinine TAF 0.01 mg/dL (95% CI 0.00-0.02) versus TDF 0.02 mg/dL (0 00-0.04) with changed rate distinction - 0.01mg/dL (95%CI - 0.03 to 0.01); p=0.32.[9]

In phase 3rd, multicenter, double-blind, RCT research of HBeAg-positive CHB patients by Chan et al., 873 patients with 25 mg TAF (n = 581) and 300 mg TDF (n = 292). With baseline HBV DNA levels (<8 log10 IU/mL vs 8 log10 IU/mL), HBV DNA fixations <29 IU/mL were accomplished in 64% (371) of subjects with TAF and 67% (195) subjects with TDF in 48 weeks (p=0.25) who demonstrated non-inferiority between the two drugs.[10] The rate decline in ALT levels at week 48 in the TAF bunch was higher (71.5%) than the TDF (66.8%). 78 patients (14%) and 34 subjects (12%) in the TAF and TDF subjects have HBeAg misfortune. Patients who had seroconversion to anti-HBe were found to be 58 (10.3%) and 23 (8.1%). The increase in serum creatinine from baseline in both groups showed that patients receiving TAF 0.01 mg/dL had a significantly smaller increase than patients receiving TDF 0.03 mg/dL (p= 0.02). A known decrease in renal filtration through the EGFR had a significantly smaller median decrease with TAF than TDF (p<0.0001).[10]

In the study of Agarwal et al., patients with CHB who were HBeAg negative and HBeAg positive were randomized 2:1. These patients got 25 mg TAF or 300 mg TDF. Examination of the adequacy of TAF and TDF at week 96 tracked down that how much HBeAg positive patients with HBV DNA < 29 IU/mL was 73% (n=423) in subjects with TAF and 75% (n=218) in subjects with TAF.[11] The subjects who got TDF, the changed distinction was - 2.2% (95% CI - 8.3% - 3.9%; p = 0.47). In the meantime, in HBeAg negative subjects, it was 90% (n=257) in subjects with TAF and 91% (n=127) in subjects with TDF. The changed contrast was - 0.6% (95% CI - 7.0% - 5.8%; p = 0.84). As an antivirus, this suggests little difference between the two drugs. Patients with TAF experienced a mean increase of 0.003 mg/dL, significantly less than the

Table 2. PICO Analysis and validity of the studies included in the analysis

Article (Years)	P	I	C	O	Random	Long Follow-up	All Patients Analyzed	Blind	Treated Equally	Similar at start
Buti et al, (2016)	+	TAF 25mg once daily	TDF 300 mg once daily	+	Yes	Yes	No	Yes	Yes	Yes
Chan et al, (2016)	+	TAF 25mg once daily	TDF 300 mg once daily	+	Yes	Yes	No	Yes	Yes	Yes
Agarwal et al, (2018)	+	TAF 25mg once daily	TDF 300 mg once daily	+	Yes	Yes	Yes	Yes	Yes	Yes
Lampertico et al, (2020)	+	TAF 25mg once daily	TDF 300 mg once daily	+	Yes	Yes	Yes	Yes	Yes	Yes

0.019 mg/dL increase experienced by subjects with TDF (p=0.001). Subjects with TAF had less decrease in middle eGFR than patients with TDF (-1.2 mL/min vs. - 4.8 mL/min, p < 0.001).[11]

A study by Lampertico et al. showed subjects with CHB with HBeAg negative and HBeAg positive were randomized 1:1. All subjects in this study were given TDF for at least 48 weeks. The two groups of patients received 25 mg of TAF in lieu of TDF or continued with 300 mg of TDF.[12] Analysis of the efficacy of TAF and TDF at week 48 found that the proportion with HBV DNA < 20 IU/mL was 63% (154 of 243) in patients receiving TAF and 62% (152 of 245) in TDF patients with a proportional difference of 1.4 % (95% CI -7.1% - 9.9%; p = 0.74). This shows that the two drugs are also not significantly different in their role as antivirals. At week 48, the median change in eGFR was +1.76 mL/min in patients receiving TAF and -1.69 mL/min in patients receiving TDF (p = 0.00034). This suggests that the safety in the group receiving TAF against the kidneys was better than in patients continuing TDF.[12]

Table 3. Validity of the studies included in the analysis

Study	Number of Subjects	TAF (doses)	TDF (doses)	Follow-up (months, weeks, years)
Buti et al, (2016)	425	25 mg	300 mg	96 weeks
Chan et al, (2016)	873	25 mg	300 mg	96 weeks
Agarwal et al, (2018)	1.298	25 mg	300 mg	96 weeks
Lampertico et al, (2020)	488	25 mg	300 mg	48 weeks

Table 4. Importance of the studies included in the analysis

Study	Overall results (treatment preference)	CER	EER	RR	ARR	RRR	NNT	Precision of the RR (95% CI)
Buti et al, (2016)	No significant difference	93 %	94%	1,011	1,8%	1,9%	0.55	-3.6 to 7.2
Chan et al, (2016)	No significant difference	67 %	64%	0.95	-3,6%	-3,7%	-0,27	-9.8 to 2.6
Agarwal et al, (2018)	Not Significant Different	75%	73%	0.97	0.02	0.026	50	-0.08 – 0.039
Lampertico et al, (2020)	Not Significant Different	62%	63%	1.01	-0.01	-0.01	100	-7.1 – 9.9

Table 5. Applicability of the studies included in the analysis

Study	Apply to Patient Care	Considering all clinically important outcomes	Benefit worth harm and cost	Assessment ofside Effects	Side Effects
Buti et al, (2016)	Yes	Yes	Yes	Yes	Headache, nasopharyngitis, upper respiratory tract infection (URTI), cough, fatigue, arthralgia, nausea, back pain
Chan et al, (2016)	Yes	Yes	Yes	Yes	URTI, nasopharyngitis, headache, cough, fatigue, diarrhea, upper abdominal pain
Agarwal et al, (2018)	Yes	Yes	Yes	Yes	Headache, Nasopharyngitis, URTI, Cough, Fatigue, Nausea, Dyspepsia, Diarrhea
Lampertico et al, (2020)	Yes	Yes	Yes	Yes	Pancreatitis, Gastroenteritis, Muscle rupture, Wrist fracture, Diabetes, Extremity pain, Breast cancer, Hepatocellular carcinoma, Malignant melanoma, Headache, Bipolar disorder, Homicidal ideation, Suicidal ideation

DISCUSSION

Based on renal function, the analyses revealed that the two listed phase 3 studies favored TAF treatment over TDF. In patients receiving treatment at week 48, the results of laboratory tests based on renal function show significant differences between both groups.[3] During treatment, no instances of proximal renal tubulopathy, including Fanconi disorder or renal disappointment, were found. The subjects also did not undergo severe renal adverse events that resulted in discontinuation of treatment on TAF or TDF for 48 weeks. The decrease in EGFR showed significantly different results between the groups given TAF and TDF in the four studies.

Lowering in EGFR with TAF was -0.6 mL/min versus -5.4 mL/min in HBeAg positive subjects ($p<0.0001$) was found in the study by Chan et al.[10] Buti et al. demonstrated a decrease of -1.8 mL/min versus -4.8 mL/min, which was noted in HBeAg negative subjects ($p = 0.004$).9 Study by Agarwal et al. showed the decrease was noted to be significantly lower in subjects with TAF versus TDF at -1.2 mL/min versus -4.8 mL/min ($p<0.001$).[11] Study by Lampertico et al. at 48 weeks, the alteration in CrCl was recorded as +1.76 mL/min after changing TDF to TAF and -1.69 mL/min in the TDF ($p=0.00034$).[12]

Based on the average change in serum creatinine in the 2 treatment groups, HbeAg positive subjects had 0.01 mg/dL compared to 0.03 mg/dL in TAF vs. TDF ($p = 0.02$), while HbeAg negative subjects had 0.02 mg/dL in TAF compared to 0.02 mg/dL in TDF ($p = 0.32$). Tremendous distinction existed between the two treatment groups was found in the middle rate change from standard, the quantitative markers of proteinuria, the ratio of urine protein to creatinine (UPCR). The modification in the UPCR mean was 6.0 mg/g and 16.5 mg/g in TAF vs TDF subjects ($p=0.010$).[5] Albeit no measurably massive contrast was found, the rate improvement from standard in the TAF subjects was lower than in the TDF. The change in middle rate in these two boundaries was lower in the TAF subjects than in the TDF subjects at week 48 ($p < 0.001$).[9]

Statistically, it showed no significant difference between therapy with TAF and TDF in suppressing viral load plasma HBV DNA<29 IU/mL. Both therapies were well tolerated, most side effects ranged from mild to moderate. All 4 studies showed the predominance of TAF over TDF regarding renal safety and lower progressive decline in renal function. TDF has almost the same effectiveness as TAF but with a better safety profile than TAF. This advantage causes TAF to be more tolerated than TDF in patients with impaired renal function. Lower plasma levels of TAF in the active form can reduce extracellular exposure to nephrons, thereby reducing renal toxicity. In addition, the administration of TAF in patients with renal dysfunction can be given without dose adjustment. Therefore, TAF shows better safety on kidney function and slows the progression of decreased kidney function and side effects on the kidneys than TDF.

Furthermore, this review does not discuss effects other than on the kidneys, such as cardiovascular and bone effects, in the long term for TAF vs TDF Further analysis comparing the effects of both treatments in a more complex and long-term manner is necessary.

CONCLUSION

Based on the study used in this Evidence-based case report, it can be concluded that the use of TAF is significantly better regarding kidney safety than TDF.

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