Evaluation Effect of Tenofovir Alafenamide (TAF) in Long-Term Therapy for Chronic Hepatitis B: A Systematic Review

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ABSTRACT

Background: *Tenofovir alafenamide (TAF) is phosphonamidate prodrug of tenofir that inhibits hepatitis B virus and HIV type-1 reverse transcription. TAF more stable form in plasma than tenofovir disoproxil fumarate (TDF) as choice treatment before. TAF in long-term treatment also significantly reduced bone mineral density (BMD) and raised serum creatinine, as well as improved markers of renal tubular function. This study aims to review the long-term therapy of TAF effect in body weight gain, BMD, renal function, lipids profile, ALT normalization, and HBeAg loss.*

Method: *The data was taken from Pubmed, ScienceDirect, and Cochrane Library. We found 363 articles from databases. The articles related to long-term therapy in chronic hepatitis-B and adjusted according to restriction criteria. Articles selection using PRISMA flowchart and quality test using GRADE method into eligible articles.*

Results: *We selected articles that eligible for systematic review with different GRADE recommendation which were 4 high-grade articles, 1 low-grade, and 1 very low-grade article. TAF in long-term therapy showed an increase in BMD ($p < 0.001$), body weight gain ($p < 0.001$), decreased renal dysfunction (CrCl; $p < 0.0001$ and GFR; $p = 0.027$), and normalized ALT ($p = 0.016$). However, lipids profile level increase that could increase risk of atherosclerosis and dyslipidemia. There was no significant in HBeAg loss.*

Conclusion: *TAF therapy is favourable therapy in long-term therapy of chronic hepatitis B patients by smaller reduce of BMD, and significant body weight gain, reduce renal dysfunction, good improvement in lipid profile and improving ALT enzymes.*

Keywords: *tenofovir alafenamide, long-term therapy, chronic, hepatitis B*

ABSTRAK

Latar belakang: *Tenofovir alafenamid (TAF) merupakan prodrug fosfonamidat dari tenofir yang menghambat virus hepatitis B dan HIV type-1 reverse transcription. TAF lebih stabil dalam plasma daripada tenofovir disoproxil fumarate (TDF) sebagai pilihan pengobatan sebelumnya. TAF dalam jangka panjang menurunkan bone mineral density (BMD) secara signifikan dan meningkatkan serum kreatinin, serta perbaikan fungsi tubular renal. Studi ini bertujuan untuk meninjau terapi jangka panjang dari efek TAF berdasar penambahan berat badan, BMD, fungsi renal, profil lipid, normalisasi ALT, dan HBeAg loss.*

Metode: *Data diambil dari Pubmed, ScienceDirect, dan Cochrane Library. Peneliti menemukan 363 artikel dari seluruh database. Seluruh artikel berhubungan dengan terapi jangka panjang pada hepatitis B kronik*

dan disesuaikan berdasarkan kriteria retriksi. Seleksi artikel menggunakan flowchart PRISMA dan uji kualitas kelayakan artikel menggunakan metode GRADE.

Hasil: *Peneliti menyeleksi seluruh artikel yang layak untuk tinjauan sistematis dengan rekomendasi GRADE yang terdiri dari 4 artikel high-grade, 1 artikel low-grade, dan 1 artikel very low-grade. TAF dalam terapi jangka panjang menunjukkan peningkatan pada BMD ($p < 0,001$), penambahan berat badan ($p < 0,001$), penurunan disfungsi renal (CrCl; $p < 0,0001$ dan GFR; $p = 0,027$), dan normalisasi ALT ($p = 0,016$). Namun, peningkatan kadar profil lipid dapat meningkatkan risiko aterosklerosis dan dislipidemia. Tidak ada perbedaan signifikan dalam HBeAg loss.*

Simpulan: *Terapi TAF merupakan terapi pilihan yang baik dalam terapi jangka panjang dari pengobatan pasien hepatitis B kronik dengan mengurangi sedikit densitas mineral tulang dan penambahan berat badan yang signifikan, penurunan disfungsi renal, perbaikan profil lipid dan memperbaiki ALT.*

Kata kunci: *tenofovir aladfenamid, terapi jangka panjang, kronik, hepatitis B*

INTRODUCTION

Chronic hepatitis B infection is a health problem experienced by people around the world and is one of the main causes of chronic liver disease, cirrhosis, and hepatocellular carcinoma (HCC).[1] Hepatitis is an inflammation of the liver that can be caused by various causes such as heavy alcohol, autoimmune, drugs, or toxins. However, the most common cause of hepatitis is a viral infection which is referred to as viral hepatitis. In the United States, the most common types of hepatitis viruses are hepatitis A, hepatitis B, and hepatitis C.[2] In Central and East Asia, Sub-Saharan Africa, and the Pacific region, the highest prevalence of hepatitis B virus infection (5-8% of adults) is predominately infected in infancy or adolescence.[3] The prevalence of hepatitis in Indonesia in 2013 was 1.2%, a double increase compared to Riskesdas in 2007 which was 0.6%. East Nusa Tenggara was the province with the highest hepatitis prevalence in 2013 which was 4.3%. Based on the ownership index quintile (which describes economic status), the lowest ownership index quintile group has the highest prevalence of hepatitis compared to other groups. Prevalence is increasing in the population aged over 15 years. Types of hepatitis that infect the population of Indonesia are hepatitis B (21.8%), hepatitis A (19.3%), and hepatitis C (2.5%).[4]

Indications for therapy for hepatitis B infection according to the 2012 hepatitis B consensus are based on a combination of four criteria, including serum hepatitis B virus DNA, HBeAg status, alanine-aminotransferase (ALT) enzyme values, and liver histology. Treatment of hepatitis B can use drugs from the interferon class or a nucleus(t)ide analogue group such as tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF). However, long-term use of TDF has been associated with a risk of renal dysfunction and decreased bone mineral density (BMD).[6] TAF with limited oral bioavailability that inhibits hepatitis B virus (HBV) and reverses transcreates human immunodeficiency virus type 1 (HIV-1). In a phase III trial, patients with viremia and HBeAg-positive or HBeAg-negative with chronic HBV infection were randomized to treatment with TAF, which significantly reduced bone mineral density and slightly raised serum creatinine, as well as improved markers of renal tubular function and bone turnover in comparison with patients receiving tenofovir disoproxil fumarate at 48 and 96 weeks.[7] TAF and TDF are both tenofovir prodrugs with the same active metabolite (tenofovir diphosphate [TFV-DP]). TAF is more stable in plasma than TDF, confers higher levels of the active TFV-DP metabolite that is phosphorylated intracellularly to target cells (HBF-infects hepatocytes and HIV-infects lymphoid cells) and is associated with relatively lower circulating levels of tenofovir with a mean of 90% compared to the therapeutically active dose of TDF (300 mg/day).[1]

This systematic review aims to determine the latest evaluation of treatment in patients with chronic hepatitis B infection using long-term tenofovir alafenamide by assessing changes in body weight gain, bone mineral density, creatinine clearance, glomerular filtration rate, lipid profile, ALT normalization, hepatitis B e antigen (HBeAg) loss and hepatitis B serum antigen (HBsAg) loss and seroconversion.

METHOD

We used data collection techniques through three e-databases, namely Pubmed, ScienceDirect, and Cochrane Library. We used the keywords "Long term" and "Tenofovir Alafenamide" and "Chronic" and

"Hepatitis B" as article searches in our e-database. In this systematic review, we selected articles that using randomized controlled trials, observational studies, or clinical trials. In addition, the inclusion criteria that we used to select articles eligible for this review included: (1) samples age 18 years (adults); (2) samples with positive HBV serologic serum; and (3) articles were published for a maximum of 5 years final. While the exclusion criteria that we used included: (1) the sample had a history of HIV disease, cardiovascular disease, or diabetes mellitus both type-1 and type-2; (2) stopping inadequate hepatitis B treatment; and (3) taking drugs that may cause drug interactions with tenofovir alafenamide such as acyclovir, bacitracin, carbamazepine, or selecoxib.

We recorded the search results that we have done from the three e-databases into Ms Excel into one. We did the double screening and then excluded those articles. After obtaining non-duplicated articles, we screened titles and abstracts that were not relevant to our restriction criteria and then excluded those articles. After getting articles that are quite relevant, we then proceed with screening the full text of each article and eliminating irrelevant articles. We have found six articles that are worthy of our use as articles that we will systematically review. We screened these articles using the steps according to the PRISMA flowchart as shown in Figure 1.

Data Items and Data Collection

Our primary outcome in this systematic review were changes in bone mineral density and changes in renal function with long-term use of tenofovir alafenamide. In addition, the secondary outcomes that we can evaluate were changes in lipid profile, normalization of ALT, weight gain, glomerular filtration rate, and HBeAg loss or HBsAg seroconversion.

To assess the evaluation of each of our outcomes, we used a previous study assessing the use of TDF and TAF as a treatment for patients with chronic hepatitis B infection and extracted data from articles that were worthy of our reviews such as articles using treatment switching from TDF to TAF in long-term use or articles comparing the use of TDF or placebo and TAF in long-term use in patients with chronic hepatitis B infection.

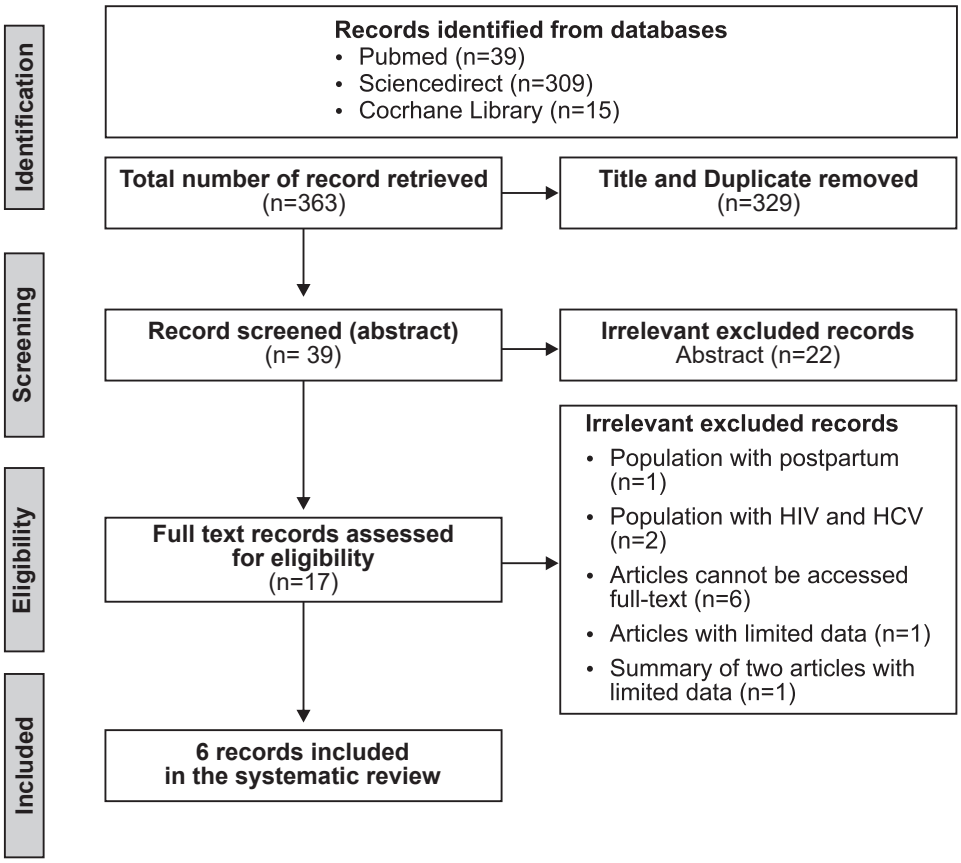

Figure 1. Flowchart diagram of articles selection process (PRISMA)

Risk of Bias and Quality of Evidence

We assessed the risk of bias and the quality of evidence in the articles that we reviewed using a system adopted by the Cochrane Collaboration called grading of recommendations, assessment, development, and evaluations (GRADE). This assessment is a method that is often used by systematic reviewers and guideline developers to assess the quality and to decide on recommendations for an intervention in a particular disease according to the value generated by GRADE.

GRADE has five steps before recommending articles that can be used as a comparison between interventions in each article. Among these measures, GRADE has assessed the risk of bias in each article in such detail as degrading the grade if there is an inconsistent result, indirectness of evidence, imprecision of results, risk of bias, and publication bias. However, each article can also be graded if there is a large magnitude of effect, all plausible confounding would reduce the demonstrated effect or increase it if no. The effect was observed, and dose-response gradient.

RESULTS

We have found 363 articles consisting of 39 articles from Pubmed, 309 articles from ScienceDirect, and 15 articles from the Cochrane library. We eliminated 329 articles with irrelevant titles and duplicate articles. We screened article abstracts and then eliminated irrelevant articles (n = 22). In the other 17 articles, we screened full text and eliminated 11 articles that were not relevant to our criteria such as articles with the postpartum population (n = 1), population with HIV and HCV (n = 2), and articles that were not accessible. Full text (n = 6), articles with limited data (n = 1), and articles with limited summary and data (n = 1).

Six articles with a total population of 3,531 patients with chronic hepatitis B infection, aged > 18 years. These articles have different study designs, including four articles with a randomized controlled trials study design, one article with a retrospective cohort study design, and one article with a multicenter retrospective. There are articles on switching therapy from TDF to TAF, articles about populations that have become resistant to entecavir (ETV) or adenovofir (ADV), and articles on TAF interventions using different doses (8 mg, 25 mg, 40 mg, or 120 mg) with a single dose TDF (300 mg). Each article has a different comparison, some using a placebo or directly with TDF.

Bone Mineral Density (BMD)

Tenofovir alafenamide as long-term treatment in patients with chronic hepatitis B infection showed that treatment with TAF was better than TDF during 48 weeks of treatment with a mean improvement in bone mineral density of 1.74% vs. -0.11% ($p < 0.0001$) and 0.66% vs. -0.51% ($p < 0.0001$) in the spine.[7] A slight decrease in bone mineral density occurred in the TAF group compared to TDF with a mean change of -0.10% vs. -1.72% ($p < 0.0001$) in the hip and -0.42% vs. -2.29% ($p < 0.0001$) in the spine.[8] Bone safety at 48 weeks in patients who underwent a treatment switch from TDF to TAF had increased mean from baseline for BMD of the spine.[9] After treatment with TAF for 96 weeks, the mean reduction in BMD was smaller than in patients receiving TDF at -0.33% (95% CI: -0.51 to -0.14; $p < 0.001$).[10] This was shown in Table 2.

Certainty assessment							№ of patients		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[intervention]	[comparison]	
1. Agarwal, Kosh., *Et al.*2017	randomised trials	not serious	not serious	not serious	not serious	none	866/1298 (66.7%)	432/1298 (33.3%)	⊕⊕⊕⊕ High
2. Yeh, Ming-Lun.,*et al.* 2021	observational studies	not serious	not serious	not serious	not serious	none	30/121 (24.8%)	91/121 (75.2%)	⊕⊕◯◯ Low
3. Suzuki, Kazuharu.,*et al.*2022	observational studies	serious	not serious	not serious	not serious	none	69/138 (50.0%)	69/138 (50.0%)	⊕◯◯◯ Very low
4. Lampertico, Pietro.,*et al.*2020	randomised trials	not serious	not serious	not serious	not serious	none	243/541 (44.9%)	245/541 (45.3%)	⊕⊕⊕⊕ High
5. Byun, Kwan Soo.,*et al.* 2021	randomised trials	not serious	not serious	not serious	not serious	none	87/174 (50.0%)	87/174 (50.0%)	⊕⊕⊕⊕ High
6. Byrne, Ruth.,*et al.*2018	randomised trials	not serious	not serious	not serious	not serious	none	581/873 (66.6%)	292/873 (33.4%)	⊕⊕⊕⊕ High

Figure 2. Grading of recommendation, assessment, development, and evaluation (GRADE)

Table 1. Characteristics study and demographic data

No	Title	Author, year	Design study	Sample	Gender		Method	Name of journal
1.	96 weeks treatment of tenofovir alafenamide vs. tenofovir disoproxil fumarate for hepatitis B virus infection	Agarwal et al, 2018	RCT	1298	819 (M)	49 (F)	Two randomized, double-blind, active-controlled international phase III trialls	Journal of Hepatology
2.	Tenofovir alafenamide for drug-resistant hepatitis B: a randomized trial for switching from tenofovir disoproxil fumarate	Byun et al, 2022	RCT	174	140 (M)	34 (F)	Multicenter, open-label, non-inferiority, randomized trials, ≥96 weeks were randomized 1:1 to switch to TAF or continue TDF	Clinical Gastroenterology and Hepatology
3.	Tenofovir alafenamide in the treatment of chronic hepatitis B virus infection: rationale and clinical trial evidence	Byrne et al, 2018	RCT	1298	-	-	Two randomized, double-blind, multinational phase III trials in patients with hepatitis B e antigen (HBeAg)-positive-negative infection	Therapeutic Advances in Gastroenterology
4.	Effect of Switching from tenofovir disoproxil fumarate to tenofovir alafenamide on lipid profiles in patients with hepatitis B	Suzuki et al, 2022	Retrospective multicentre	99	45 (M)	24 (F)	Retrospective multi-centre study, recruited between 2016 and 2020	PLOS ONE
5.	Switching from tenofovir disoproxil fumarate to tenofovir alafenamide in virologically suppressed patients with chronic hepatitis B: a randomised, double-blinde, phase 3, multicentre non-inferiority study	Lampertico et al, 2020	RCT	541	345 (M)	96 (F)	Randomised, multicentre, double-blind, phase 3 non-inferiority study	Lancet Gastroenterol Hepatol
6.	Body weight changes in treated hepatitis B patients switching to tenofovir alafenamide	Yeh et al, 2021	Retrospective cohort	121	87 (M)	34 (F)	Retrospective cohort study with patient were switched to TAF after 12 months of treatment	ScienceDirect

Creatinine Clearance (CrCl) and Glomerulus Filtration Rate (GFR)

Changes in creatinine clearance by the Cockcroft-Gault method, and TAF treatment showed good results, in none of the patients associated with serious renal side effects or proximal tubulopathy including Fanconi syndrome. A median increase from baseline was observed in the TAF group at week 48 with a significant difference of 0.94% vs -2.74% ($p < 0.001$) or +1.76 (IQR = -1.07 to 7.35) mL/min ($p = 0.00034$).[7] At 96 weeks of treatment, TAF showed a lower median value with decreased GFR of 1.2 mL/min vs 4.8 mL/min ($p < 0.001$) compared to TDF. The increase in mean creatinine from baseline in patients treated with TAF also had a significantly smaller value compared to TDF at 0.003 mg/dL vs 0.019 mg/dL ($p = 0.001$).[8,10] Significantly the mean increase in creatinine clearance was high in the TAF group compared to TDF at week 48 in patients experiencing resistance to ETV and ADV drugs, which was 6.9 mL/min/1.73 m^2 vs 3.2 mL/min/1.73 m^2 ($p = 0.047$). TAF also showed a significantly greater median percentage decrease in urine protein in creatinine ratio than the TDF group (-190% vs -11.1%; $p = 0.01$).[9] The change in treatment from TDF to TAF showed significant results with an assessment from baseline (pre-TDF) to post-TDF and then changed from pre-TAF to post-TAF, namely from 70.5 ± 17.3 mL/min/1.73 m^2 (pre-TDF) to 68.2 ± 16.2 mL/min/1.73 m^2 then stopped for switching treatment with TAF from 64.7 ± 13.4 mL/min/1.73 m^2 to 65.3 ± 15.1 mL/min/1.73 m^2 ($p < 0.001$).[11] Significant results were also obtained at switching treatments with mean serum creatinine values of 0.92 ± 0.24 mg/dL at the 3rd month, 0.95 ± 0.23 mg/dL at the 6th month ($p = 0.039$), 0.94 ± 0.22 mg/dL at the 9th month, and 0.92 ± 0.22 mg/dL at 12th months.[12] This was shown in Table 2.

Table 2. Evaluation results of tenofovir alafenamide treatment

No	Author, year	Intervention	Comparison	Result
1.	Agarwal et al, 2018	Tenofovir alafenamide (25 mg)	Tenofovir disoproxil fumarate (300 mg)	• After 96 weeks, at BMD hip (TAF) -33% (95% CI: -0.51 to -0.14) and spine (TAF) -0.75% (95% CI: -1.01 to -0.49), P < 0.001 • serum creatinine from baseline, mean increase of 0.003 mg/dL in TAF (p < 0.001) and smaller median decrease in eGFR in TAF -1.2 mL/min (p < 0.001) • ALT was 75% vs 68%, difference 8% (95% CI: 1.2 to 14.7; p = 0.017) in patient HBeAg-positive (TAF) and 52% vs 42%, difference 10.6% (95% CI: 3.6 to 17.6; p = 0.003) • HBeAg loss among HBeAg-positive receiving TAF 22% (123/565) not significant compared to TDF 18% (51/285), but HBsAg seroconversion 1% (TAF) or 7 of 576 patients and 4 of 288 patients
2.	Byun et al, 2022	Tenofovir alafenamide (25 mg)	Tenofovir disoproxil fumarate (300 mg)	• After 96 weeks, at BMD spine (TAF) 1.8 ± 4.9 g/cm^2 (p < 0.02) and hip (TAF) -0.2 ± 4.0 g/cm^2 • Higher increase in CrCl at week 48 (6.9 mL/min/1.72 m^2; p = 0.47) • Total cholesterol 18 mg/dL (p<0.01), LDL cholesterol 13 mg/mL (p < 0.01), and HDL cholesterol 7 mg/dL (p < 0.01) in TAF group • Mean body weight increase 0.71 ± 2.39 kg in TAF at week 48
3.	Byrne et al, 2018	Tenofovir alafenamide (25 mg)	Tenofovir disoproxil fumarate (300 mg)	• After 48 weeks, at BMD hip (TAF) mean change -0.10% and spine -0.42% (p < 0.0001) compared with TDF in patient HBeAg-positive, than in patient HBeAg-negative is -0.29% for hip and -0.88 % for spine (p < 0.0001) • After 96 weeks, BMD hip (TAF) improved -2.7% to -2.1% (p < 0.001) and BMD spine -3.1% to 1.6% (p < 0.001) • Median change in eGFR significantly smaller in the TAF recipients compared with TDF (HbeAg-positive -0.6 mL/min, p < 0.0001; and HBeAg-negative -1.8 mL/min, p < 0.004) and increase in cratinine from baseline TAF smaller than TDF 0.003 mg/dL (p = 0.001)
4.	Suzuki et al, 2022	TAF (25 mg)	TDF (300 mg) switch TAF (25 mg)	• After 6-12 months, eGFR showed a change from 64.7 ± 13.4 mL/min/1.73 m^2 to 65.3 ± 15.1 mL/min/1.73 m^2 (P < 0.001) • After 6-12 months, ALT normalization showed a change from 26 ± 25 IU/L to 21±10 IU/L (p < 0.001)
5.	Lampertico et al, 2020	Tenofovir alafenamide (25 mg)	Tenofovir disoproxil fumarate (300 mg)	• After 48 weeks, the decrease in creatinine clearance was significant p < 0.001 compared to TDF, change from baseline in creatinine clearance by Cockcroft-Gault +1.76 mL/min in the TAF group
6.	Yeh et al, 2021	Tenofovir alafenamide (25 mg)	Tenofovir disoproxil fumarate (300 mg)	• Change in mean eGFR at 3 months 88.2 ± 18.8 mg/dL, p < 0.030; 6th month 85.1 ± 18.5 mg/dL; 9th month 85.5 ± 16.5 mg/dL; and 12th month 87.2 ± 17.5 mg/dL

BMD: bone mineral density, TAF: tenofovir alafenamide, ALT: alanine aminotransferase, GFR: glomerular filtration rate, HBeAg: hepatitis B e antigen, HBsAg: hepatitis B serum antigen

Lipid Profile

Changes in the mean lipid profile in patients with chronic hepatitis B infection with significant TAF of both total cholesterol (p < 0.001), low density lipoprotein (LDL) cholesterol (p < 0.001), and total high density lipoprotein (HDL) cholesterol (p < 0.001) for 48 weeks. However, the ratio of total HDL cholesterol decreased slightly in the two treatment groups without any significant difference (-0.27% ± 20.0 in the TAF group vs -1.38% ± 15.3 in the TDF group.[9] This was shown in Table 2.

Body Weight Gain

Post-hoc analysis showed that the outcome of switching treatment from TDF to TAF was not significantly increased in weight from pre-switch to six months after switching (66 ± 12.5 kg vs. 66.9 ± 12.9 kg, p = 0.427). However, one year after the TAF switch, the patient's weight increased to 67 ± 12.6 kg, which was significantly different from the pre-switch (p = 0.001) and six months after the switch (p = 0.010). Paired T-test analysis showed a significant increase in body weight from 66.4 ± 11.8 kg pre-switch to 67.8 ± 12.3 kg after one year of switching with TAF (p < 0.001).[12] The mean weight increase in patients who did receive TAF from the start was 0.71 ± 2.39 kg after 48 weeks of treatment. However, in the number of patients who gained 1.0 kg weight at week 48 from baseline, there was no significant difference between the TAF and TDF groups.[9] This was shown in Table 2.

ALT Normalization

HBeAg positive patients with high ALT at baseline who had normal ALT at week 96 of TAF treatment were 75% compared to 68% with TDF, the 8% difference was statistically significant (95% CI: 1.2% to 14.7%; p = 0.017). Patients who received TAF had higher normalized ALT scores than patients who received TDF at the visit after 8 weeks of treatment. Whereas in HBeAg negative patients, the proportion of ALT

was high from baseline and had normal ALT after 96 weeks of treatment with TAF was 81% compared to 71% with TDF. The 9.8% difference was statistically significant (95% CI: 0.2% to 19.3%; p = 0.038).[10] The decrease in ALT occurred 6-12 months after treatment with TAF after switching from TDF. At pre-TDF 42 ± 38 IU/L to 27 ± 13 IU/L after 6-12 months with TDF treatment while the transition begins with pre-TAF values 26 ± 25 IU/L post-TDF to 21 ± 10 IU/L after 6-12 months of treatment with TAF (p < 0.01).[11] This was shown in Table 2.

HbeAg and HbsAg Loss and Seroconversion

The value of HBeAg loss between HBeAg positive patients who received TAF was 22% at week 96 which was not significantly different from the TDF group, which was 18%. However, the seroconversion HBeAg value was significantly higher in the TAF group than in the TDF group. In both groups, the HBsAg loss at week 96 was 1% or 7 of 576 with patients receiving TAF and 4 of 288 with patients receiving TDF. Patient who was receiving TAF, tested negative for HBsAg at week 64 and achieved seroconversion to anti-HBs at week 80 which persisted through week 96.[10] In the 25 patients with HBeAg serotype at TAF switch, two (8.0%) developed HBeAg loss, one in the third month and one in the 12th month. None experienced HBeAg seroconversion.[12] This was shown in Table 2.

DISCUSSION

Chronic hepatitis B virus infection is a global public health threat that causes morbidity and mortality of the liver disease. Hepatitis B can infect at birth or later through person-to-person transmission.[13] Currently, there are two treatment options for chronic hepatitis B: interferon and oral antiviral agents. Treatment with oral antiviral agents has been successful in maintaining viral suppression in chronic hepatitis B patients, an effect associated with a reduction in long-term complications.[1]

TAF is a drug indicated for adult patients with chronic hepatitis B infection with compensatory liver disease, with an oral dose of 25 mg per day. TAF is a more stable prodrug in plasma than TDF, thereby reducing plasma exposure to tenofovir. This reduction in tenofovir exposure may reduce the long-term toxicity of TDF such as nephrotoxicity and decreased bone mineral density.[14]

Minimal reduction in bone mineral density or improvement in bone mineral density after treatment with tenofovir alafenamide had good results in four articles with high GRADE quality. This proves that tenofovir alafenamide in long-term use, whether used since the beginning of therapy in chronic hepatitis B patients or switching treatment from tenofovir disoproxil fumarate is very good and can be used as a treatment option. In a study by Agarwal et al (2018), the percentage reduction in hip bone mineral density was milder -0.33% (95% CI: -0.51 to -0.14) for patients receiving TAF (25 mg) for 96 weeks compared to TDF (300 mg) - 2.51% (95% CI: -2.82 to -2.21). If in the spine the decrease in bone mineral density is lighter and the same as in the hip, it is -0.75% (95% CI: -1.01 to -0.49).

In the study by Byrne et al (2018), an evaluation of TAF was carried out at 48 and 96 weeks in the group with chronic hepatitis B infection and positive HBeAg results were obtained at 48 weeks showing patients who received TAF (25 mg) had higher values than those who received TAF (25 mg). Significantly high reduction in BMD was very small compared to patients receiving TDF (300 mg) -0.10% versus -1.72%, p < 0.0001 in the hip and -0.42% versus -2.29% in the spine. The same thing happened in HBeAg negative patients, namely -0.29 versus -2.16% in the hip, p<0.0001 and -0.88 versus -2.51% in the spine, p<0.0001. At the 96th week evaluation, good results were also observed with TAF treatment of -0.33% versus -2.52% for the hip and -0.75% versus -2.59% for the spine compared with TDF. Further evaluation, significant improvement in bone mineral density was shown at week 120 (-2.7% to -2.1%; p < 0.001) in hip and (-3.1% to -1.6%; p < 0.001) in patients who were switched from TDF treatment to TAF.

A study by Byun et al (2022) showed that patients with chronic hepatitis B infection with drug resistance ETV or ADV had a good improvement in mineral density with TAF treatment (25 mg) after 96 weeks of treatment from baseline with a change in the mean BMD of the spine. 1.8 ± 4.9 g/cm^2 compared to TDF (300 mg) which decreased from baseline with an average change of BMD 0.2 ± 4.2 g/cm^2 (p < 0.02). Meanwhile, the hip was -0.2 ± 4.0 g/cm^2 with TAF and -0.3 ± 4.9 g/cm^2 with TDF. The same results also occurred in the study by Lampertico et al (2020) which was carried out with BMD evaluation at 24 and 48 weeks. The mean change from baseline at week 24 has shown improvement in BMD in the TAF group compared to the TDF group, the last evaluation occurred at week 48 were the mean change from baseline was 1.74% versus -0.11% in the spine and 0.66% versus -0.51% on hip.

In this study, an increase in the mean BMD on TAF treatment in both the hip and spine after treatment of TDF and TAF, this very positive change we observed in previous studies is still consistent. At 96 weeks of treatment, the results were consistent with the results of the treatment at 48 weeks in patients who received treatment with TAF in the improvement of hip and spine bone mineral density.[8] Patients with chronic hepatitis B infection with drug resistance ETV or ADV had better outcomes after switching to TAF, a very large change in hip BMD compared to the spine after 48 weeks of treatment.[9] The hip BMD showed that a significant decrease occurred continuously in TDF compared to TAF from week 48 to week 96, this needs to be followed up with comprehensive data observations to prevent a decrease in BMD in patients so that meaningful clinical goals are obtained because such bone fracture will increase when the BMD decreases in the patient.[10] The effect of tenofovir is related to osteoblast and osteoclast activity. Bone biomarkers underwent minimal changes in patients receiving TAF, due to the lower effect of the catabolic window on the bone turnover when compared to TDF.[6] One of the mechanisms by which TDF is associated with bone loss is associated with impaired renal tubular handling of phosphate.[15]

In the study of Lampertico et al (2020), there were no patients with renal-related adverse events, serious renal adverse events, or proximal tubulopathy including Fanconi syndrome. A median baseline increase in creatinine clearance was observed in the tenofovir alafenamide group compared with the tenofovir disoproxil fumarate group with a significant reduction at 48 weeks ($p < 0.001$). At 48 weeks, the median change from baseline in creatinine clearance with Cockcroft-Gault was +1.76 (IQR = -1.07 to 7.35) mL/min in the TAF group and -1.69 (-7.30 to 1.98) mL/min in the TDF group ($p = 0.00034$). At week 48, the median change in eGFR was significantly smaller in TAF recipients compared to TDF recipients (HBeAg-positive: -0.6 versus -5.4 mL/min, $p < 0.0001$; HBeAg-negative: -1.8 versus -4.8 mL/min, $p < 0.004$). The impact of TAF was milder than TDF on renal parameters continued at week 96. The mean increase in creatinine from baseline of 0.003 mg/dL in patients receiving TAF was significantly smaller than the increase of 0.019 mg/dL in patients receiving TDF ($p = 0.001$). Patients receiving TAF had a significantly smaller median reduction in eGFR by Cockcroft-Gault than patients receiving TDF (1.2 mL/min versus 4.8 mL/min, $p < 0.001$).[8,9,10]

Changes in eGFR both on TAF treatment since the beginning and switching treatment from TDF to TAF showed very significant results with a pre-administration evaluation with post-administration evaluation. In the group that started treatment with TAF, pre-administration observations showed that the e-GFR value was 65.4 ± 18.8 mL/min/1.73 m^2 to 64.9 ± 18.4 mL/min/1.73 m^2 after 6-12 months of treatment (post-administration). In the group that started treatment with TDF, pre-administration observations obtained e-GFR values of 70.5 ± 17.3 mL/min/1.73 m^2 to 68.2 ± 16.2 mL/min/1.73 m^2 after 6-12 months of treatment, then treatment was changed to TAF and observed values. The pre-administration e-GFR value was 64.7 ± 13.4 mL/min/1.73 m^2 to 65.3 ± 15.1 mL/min/1.73 m^2 (post-administration) after 6-12 months of treatment with TAF ($p < 0.001$).[11] The mean serum creatinine at the time of treatment switching was 0.92 ± 0.22 mg/dL to 0.92 ± 0.24 mg/dL in the 3rd month, then 0.95 ± 0.23 mg/dL in the 6th month, and 0.94 ± 0.22 mg/dL at the 12th month ($p < 0.039$). Changes in the mean e-GFR also occurred starting at the sixth month ($p < 0.030$) when switching drugs, 85.1 ± 18.5 mg/dL at the 6th month, 85.5 ± 16.5 mg/dL at the 9th month, and 87.2 ± 17.5 mg/dL in the 12th month.[12]

Changes in lipid profile (total cholesterol, LDL cholesterol, and HDL cholesterol) were significant from baseline ($p < 0.01$) in the TAF group at 18 mg/dL (IQR = 2.3 to 31.8) compared to TDF group at 1 mg/dL (IQR = -9 to 10) on the total cholesterol, ($p < 0.01$) in the TAF group at 13 mg/dL (IQR = 5 to 24) versus TDF group at 1 mg/dL (IQR = -9 to 11) on the LDL cholesterol, ($p < 0.01$) in the TAF group at 7 mg/dL (IQR = 0 to 11) versus TDF group at 1 mg/dL (IQR = -3 to 5) on the HDL cholesterol.[9] The increased lipid profile in the TAF group compared with TDF because high serum TDF in plasma has been associated with decreased lipids in patients treated with TDF. The effect of altered metabolism of TAF switching should be investigated further in studies with longer follow-up and surveillance of other risk factors.[9]

Post hoc analysis using Bonferroni correction showed that TAF switching was not significantly associated with weight gain after six months of treatment switching (66.4 ± 12.5 kg vs 66.9 ± 12.9 kg, $p = 0.427$). However, after one year of using TAF, weight gain was 67.8 ± 12.6 kg ($p = 0.001$) compared to baseline.[12] In the initial TAF treatment, the mean weight gain increased by 0.71 ± 2.39 kg in the TAF group ($p < 0.01$) which then decreased by 0.37 ± 3.12 kg after 48 weeks of treatment.[9] However, patients with

a weight gain of 1.0 kg after 48 weeks of treatment from baseline showed no significant difference between the two groups (37 vs 28, p = 0.83). Nonetheless, it is unclear whether TAF has the weight-gaining effect or TDF has a wight-losing effect. The underlying mechanisms and long-term clinical outcome of weight change with TAF treatment are unclear and require additional studies.[1]

Results were significant in the HBeAg positive group of patients on TAF (25 mg) treatment after treatment for 96 weeks with a difference of 8% (95% CI: 1.21 to 4.7) with p = 0.017 compared to TDF (300 mg) and in the HBeAg negative group of patients on TAF (25 mg) treatment after 96 weeks of treatment, a difference of 9.8% (95% CI: 0.2 to 19.3) with p = 0.038 compared to the TDF group (300 mg).[10] The decrease in serum HBsAg levels may be accelerated by the elongation of the nucleo(t)ide analogue treatment period which may be due to the ageing of the patient. Nucleo(t)ide analogues directly induce IFN-λ3 on intestinal mucosal cells aiming to reduce HBsAg production by hepatotoxic cells in patients with hepatitis B virus infection and reduce HBsAg antigen production in a dose-dependent manner resulting in the decreased effect of HBsAg by hepatotoxic cells.[16]

The consistency of the effects over time, ALT normalization occurred very high in TAF treatment compared to TDF after 8 weeks of treatment, this could be due to a problem or not due to some unknown population randomization. Several hypotheses have been discussed about this unexpected effect and further investigation into the mechanism of this effect is needed.[10] Treatment with TAF from the start and the switch from TDF to TAF also got significant results, on pre-administration evaluation with TAF normalized ALT values from 27 ± 19 IU/L to 22 ± 9 IU/L after 6-12 months of treatment (post-administration). Meanwhile, the TDF group which was then replaced with TAF showed significant results with pre-administration evaluation after treatment with TDF 26 ± 25 IU/L to 21 ± 10 IU/L after treatment with TAF (post-administration) with p < 0.001.[11]

The response was similar between treatment with TAF compared with TDF in the HBeAg positive group. Values of HBeAg loss and anti-HBeAg seroconversion were numerically higher in patients receiving TAF than in TDF and in both groups, the increase from week 48 to week 96 is consistent with results in previous studies.[10]

CONCLUSION

Tenofovir alafenamide therapy is a favourable therapy compared to TDF in the long-term treatment of chronic hepatitis B patients by increasing bone mineral density, and body weight, reducing the risk of renal dysfunction (creatinine clearance and eGFR) and improving ALT enzymes. However, it needs more investigation and a large randomized study about the lipid profile and ALT normalization to explain the unexpected effect of tenofovir alafenamide.

REFERENCES

1. Buti M, Riveiro-Barciela M, Esteban R. Tenofovir alafenamide fumarate: a new tenofovir prodrug for the treatment of chronic hepatitis B infection. J Infect Dis 2017;216:S792–6.
2. Mehta P, Reddivari AKR. Hepatitis. National Library of Medicine (Statpearls). 2021. [serial online] [cited 2022 Oct 18] Available from: https://www.ncbi.nlm.nih.gov/books/NBK554549/.
3. Tang LSY, Covert E, Wilson E, Kottilil S. Chronic hepatitis B infection a review. J Am Med Assoc 2018;319:1802–13.
4. Infodatin Kemenkes. Situasi penyakit hepatitis B di Indonesia tahun 2017. J Chem Inf Model 2017;53:1689–99.
5. Gani RA, Hasan I, Djumhana A, Setiawan PB. In Akbar N, Prasetya IB, Indriani A, eds. Konsensus Hepatitis B. 2nd ed. Jakarta: Perhimpunan Peneliti Hati Indonesia. 2012:II.p.1–45.
6. Lee BT, Chang M, Lim C, Bae HS, Fong TL. Bone and renal safety profile at 72 weeks after switching to tenofovir alafenamide in chronic hepatitis B patients. JGH Open 2021;5:258–63.
7. Lampertico P, Buti M, Fung S, Ahn SH, Chuang WL, Tak WY, et al. Switching from tenofovir disoproxil fumarate to tenofovir alafenamide in virologically suppressed patients with chronic hepatitis B: a randomised, double-blind, phase 3, multicentre non-inferiority study. Lancet Gastroenterol Hepatol 2020;5:441–53.
8. Byrne R, Carey I, Agarwal K. Tenofovir alafenamide in the treatment of chronic hepatitis B virus infection: rationale and clinical trial evidence. Therap Adv Gastroenterol 2018;11:1–12.
9. Byun KS, Choi J, Kim JH, Lee YS, Lee HC, Kim YJ, et al. Tenofovir alafenamide for drug-resistant hepatitis B: a randomized trial for switching from tenofovir disoproxil fumarate. Clin Gastroenterol Hepatol 2022;20:427-37.
10. Agarwal K, Brunetto M, Seto WK, Lim YS, Fung S, Marcellin P, et al. 96 weeks treatment of tenofovir alafenamide vs. tenofovir disoproxil fumarate for hepatitis B virus infection. J Hepatol 2018;68:672–81.
11. Suzuki K, Suda G, Yamamoto Y, Abiko S, Kinoshita K, Miyamoto S, et al. Effect of switching from tenofovir disoproxil fumarate to tenofovir alafenamide on lipid profiles in patients with hepatitis B. PLoS One 2022;17:1–14.
12. Yeh ML, Liang PC, Trinh S, Huang CI, Huang CF, Hsieh MY, et al. Body weight changes in treated hepatitis B patients switching to tenofovir alafenamide. J Formos Med Assoc 2022;121:1273-82.

13. Seto WK, Lo YR, Pawlotsky JM, Yuen MF. Chronic hepatitis B virus infection. Lancet 2018;392:2313–24.
14. Childs-Kean LM, Egelund EF, Jourjy J. Tenofovir alafenamide for the treatment of chronic hepatitis B monoinfection. Pharmacotherapy 2018;38:1051–7.
15. Fong TL, Lee BT, Tien A, Chang M, Lim C, Ahn A, et al. Improvement of bone mineral density and markers of proximal renal tubular function in chronic hepatitis B patients switched from tenofovir disoproxil fumarate to tenofovir alafenamide. J Viral Hepat 2019;26:561–7.
16. Uchida Y, Nakao M, Yamada S, Tsuji S, Uemura H, Kouyama JI, et al. Superiority of tenofovir alafenamide fumarate over entecavir for serum HBsAg level reduction in patients with chronic HBV infection: a 144-week outcome study after switching of the nucleos(t)ide analog. PLoS One 2022;17:1–16.