TREATMENT OUTCOME OF TENOFOVIR DISOPROXIL FUMARATE (TDF) AMONG CHRONIC HEPATITIS B PATIENTS: A RETROSPECTIVE REVIEW IN HOSPITAL SULTANAH NUR ZAHIRAH (HSNZ)

DR. AHMAD WAFIY BIN WAMZAH

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LIST OF ABBREVIATIONS

ADV	Adefovir dipivoxil
cccDNA	covalently closed circular DNA
CHB	Chronic Hepatitis B
CVR	Complete virological response
ETV	Entecavir
HCC	Hepatocellular carcinoma
HIS	Health Information System
HSNZ	Hospital Sultanah Nur Zahirah
LAM	Lamivudine
MOH	Ministry of Health
PVR	Partial virological response
TDF	Tenofovir Disoproxil Fumarate
WHO	World Health Organization

ABSTRAK

Latar belakang: Tenofovir disoproxil fumarate (TDF) adalah antara analog nukleotida penghalang tinggi yang kini lebih disukai sebagai terapi pertama dalam pesakit hepatitis B kronik. Keselamatan dan keberkesanannya telah disahkan dalam 2 ujian klinikal fasa III. Bagaimanapun, tiada laporan telah diterbitkan mengenai pengalaman dengan TDF di kalangan penduduk Asia Tenggara termasuk Malaysia. Objektif kajian adalah untuk menentukan peratusan pesakit hepatitis B kronik yang mencapai penindasan virologi lengkap selepas dirawat dengan TDF pada 12 bulan dan 24 bulan terapi di Hospital Sultanah Nur Zahirah dan untuk mengenal pasti faktor yang berkaitan dengan penindasan virologi yang lengkap.

Metodologi: Ini adalah kajian kohort menggunakan data sekunder, yang melibatkan pesakit hepatitis B kronik yang dirawat dengan Tenofovir Disoproxil Fumarate (TDF) sekurang-kurangnya untuk tempoh 3 bulan, antara 1 Januari 2017 hingga 31 Disember 2021. Kadar pesakit hepatitis B kronik yang mencapai tindak balas virologi lengkap (CVR) pada akhir 12 dan 24 bulan terapi dinilai. Selain itu, perkaitan tindak balas virologi lengkap dengan faktor *clinicodemographic*, hasil klinikal (komplikasi berkaitan sirosis hati, perkembangan karsinoma hepatoselular), tindak balas biokimia, dan status survival juga dianalisa.

Keputusan: Sebanyak 108 pesakit yang memenuhi kriteria inklusi telah dikenalpasti. 60.5% (49 daripada 81) pesakit mencapai tindak balas virologi lengkap pada 12 bulan terapi TDF dan 76 daripada 90 (84.4%) pesakit mencapai tindak balas virologi lengkap pada akhir 24 bulan terapi TDF. Analisis menggunakan regresi logistik berganda menunjukkan kehadiran antigen HBeAg sebagai satu-satunya faktor yang mempunyai perkaitan yang signifikan dengan penindasan virologi yang lengkap. (OR= 8.246, 95% CI: 2.093 – 32.487, *p-value* = 0.003). Menggunakan ujian *chi-square*, persatuan penindasan virologi lengkap pada 24 bulan terapi TDF ditunjukkan secara statistik signifikan (nilai p <0.001) dengan perkembangan pendarahan varises, asites, peritonitis bakteria spontan, ensefalopati hepatik, karsinoma hepatoselular, dan

kelangsungan hidup secara keseluruhan. Normalisasi tahap ALT ditunjukkan secara signifikan dikaitkan dengan penindasan virologi lengkap pada kedua-dua 12 bulan dan 24 bulan terapi TDF.

Kesimpulan: Pengalaman kami daripada kajian ini menunjukkan bahawa TDF adalah terapi yang berkesan untuk pesakit hepatitis B kronik dalam kalangan penduduk kita. Induksi penindasan jangka panjang DNA HBV harus menjadi titik akhir utama merawat pesakit Hepatitis B kronik kerana ini dikaitkan secara signifikan dengan hasil klinikal; mencegah perkembangan penyakit selanjutnya dan perkembangan karsinoma hepatoselular, dengan itu meningkatkan kemandirian keseluruhan.

Kata kunci: *CVR, TDF, tahap DNA HBV, sirosis hati, karsinoma hepatoselular*

ABSTRACT

Background: Tenofovir disoproxil fumarate (TDF) is among the high barrier nucleotide analogue currently preferred as first-line therapy in chronic hepatitis B patients. Its safety and efficacy have been confirmed in 2 phase III clinical trials. However, no reports have been published on the experience with TDF among Southeast Asian populations, including Malaysia. The objectives of the study are to determine the proportion of chronic hepatitis B patients achieving complete virological suppression after being treated with TDF at 12 months and 24 months of therapy in Hospital Sultanah Nur Zahirah and to identify factors associated with the complete virological suppression.

Methods: This was a retrospective cohort study using secondary data, which involved chronic hepatitis B patients treated with Tenofovir Disoproxil Fumarate (TDF) for at least 3 months, between 1st January 2017 and 31st December 2021. The proportion of chronic hepatitis B patients who achieved complete virological response (CVR) at the end of 12 and 24 months of therapy was evaluated. Additionally, the association of complete virological response with clinico demographic factors, clinical outcome (liver cirrhosis-related complications, development of hepatocellular carcinoma), biochemical response, and survival status was also analysed.

Result: 108 patients who fulfilled the inclusion criteria were identified. 60.5% (49 out of 81) patients achieved complete virological response at 12 months of TDF therapy, and 76 out of 90 (84.4%) patients achieved complete virological response at the end of 24 months of TDF therapy. Analysis using multiple logistic regression showed the presence of HBeAg antigen as the only factor associated significantly with complete virological suppression. (OR= 8.246, 95% CI: 2.093 – 32.487, *p*-value = 0.003). Using chi-square tests, the association of complete virological suppression at 24 months of TDF therapy was shown to be statistically significant (*p*-value < 0.001) with the reduction of liver cirrhosis complications, namely variceal bleeding,

ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, and the incidence of hepatocellular carcinoma. Normalisation of ALT levels was shown to be significantly associated with complete virological suppression at 12 months and 24 months of TDF therapy.

Conclusion: Our experience from this study shows that TDF is an effective therapy for chronic hepatitis B patients in our population. Induction of long-term suppression of HBV DNA should be the primary endpoint of treating chronic Hepatitis B patients as this is significantly associated with favourable clinical outcomes, preventing further disease progression and development of hepatocellular carcinoma, thus improving overall survival.

Keywords: *CVR, TDF, HBV DNA levels, liver cirrhosis, hepatocellular carcinoma*

CHAPTER 1: INTRODUCTION

Hepatitis B infection remains a global public health burden with significant morbidity and mortality. The World Health Organization (WHO) estimates that 296 million people were living with chronic hepatitis B infection in 2019, with an estimated 1.5 million new infections yearly. WHO also estimated that in 2019, hepatitis B resulted in 820 000 deaths, primarily due to complications from liver cirrhosis and hepatocellular carcinoma (1).

In Malaysia, up till 2017, 35 861 cases had been reported to the Ministry of Health (MOH) (2). According to the ministry report, 5% of the Malaysian population lives with hepatitis B (3). The incidence rate of hepatitis B also increased from 2.26 per 100,000 in 2010 to 12.65 per 100,000 in 2015 (1) and is projected to increase further between 2010 and 2040 (4).

Managing chronic hepatitis B patients is challenging due to the lack of direct effects of currently available therapies on the viruses' covalently closed circular DNA (cccDNA). Besides that, integrated HBV DNA into the host genome is another barrier that causes the Hepatitis B virus to be more challenging to eradicate. (5). Treatment goals in managing chronic hepatitis B patients remain to improve survival by preventing progression to liver cirrhosis and the development of hepatocellular carcinoma. To achieve this, the European Association for the Study of the Liver (EASL) recommends the induction of long-term virological suppression of HBV DNA as the primary endpoint of the therapy. (6)

Complete virological response as the primary endpoint in managing chronic Hepatitis B

REVEAL-HBV study demonstrated that HBV DNA level is a prominent risk predictor of HCC development independent of HBeAg status, ALT levels, and the presence of cirrhosis (7). The introduction of effective antiviral therapy will inhibit the viral replication process, thus eliminating chronic HBV-induced necroinflammation and progressive fibrosis process, later reducing the HCC risk. In an earlier randomised controlled trial conducted by Liaw et al. (2004), the introduction of Lamivudine therapy, an older nucleotide analogue, to patients with cirrhosis or advanced fibrosis and active liver disease showed a reduction in disease progression and a significant risk reduction of HCC development. With a mean treatment duration of 3 years, lamivudine reduced the HCC risk by 51%, compared to the placebo group. (hazard ratio [HR] = 0.49; p = 0.047) (8)

However, maintaining virological remission after initial antiviral therapy is another important parameter in reducing HCC incidence. The HCC incidence was less frequent in patients remaining in virological remission than in those with viral breakthrough or no response. (2.3% versus 7.5%, $p<0.001$). The HCC rate was also significantly higher in lamivudine resistance cases. (7.1% versus 3.8%, $p<0.001$). (9). Due to the high resistance rate of earlier nucleotide analogues, namely lamivudine, adefovir, and telbivudine, they are no longer recommended as first-line treatment in chronic hepatitis B (6)

Efficacy of tenofovir disoproxil fumarate (TDF) for treatment of chronic Hepatitis B in real-world experience

Tenofovir disoproxil fumarate (TDF) is among potent nucleotide analogues with a high barrier to resistance which is currently recommended as first-line therapy in chronic hepatitis

B patients. TDF resistance was not observed in chronic Hepatitis B patients receiving treatment for up to 6 years (10)

Carey et al. describe a higher proportion of achieved complete viral suppression in the TDF group compared with LAM+ADV and ETV groups at the first 3 months of therapy: 78% vs 48% and 53%, $p<0.01$, but were similar proportion at 12 months: 80% vs 73% and 76%. (11). In another study done by Calvin et al. among Asian-American populations, 74 patients (82% overall; 70% HBeAg-positive and 100% HBeAg-negative) had HBV DNA <400 copies/mL at 48 weeks of TDF therapy. Meanwhile, Lovett et al. conducted a retrospective analysis among Australian populations, which showed that 77 out of 92 patients (83.7%) achieved complete virological suppression by 36 weeks (12)

There were few real-world studies conducted among Asian populations. Zheng et al. conducted a 2-year Prospective Study in China from January 2016 to May 2017 in which >95% of patients (out of 105 patients) achieved complete virological response by 96 weeks (13). In a recently published retrospective study conducted in South Korea, 127 out of 154 (82.5%) TDF-treated patients achieved complete virological response 48 weeks after administration (14).

Few factors were found to be associated with complete virological suppression. Multivariate analysis done by Lovett et al. showed a significant relationship between virological suppression at the end of follow-up with baseline HBV DNA level and the presence of HBeAg before embarking on therapy. However, no significant relationship was proven between virological suppression and treatment experience, age, and baseline ALT levels (12). The retrospective study done by Zheng et al. also showed no difference between treatment-naive and treatment-experienced in achieving virological response (13).

Despite the availability of potent nucleotide analogues, chronic hepatitis B patients may still develop hepatocellular carcinoma (HCC). In CHB patients treated with the currently

recommended first-line antivirals entecavir or tenofovir, the observed HCC risk ranges from 0.01 to 1.4% in patients without cirrhosis and from 0.9 to 5.4% in those with cirrhosis (15). This may support that the current treatment of chronic hepatitis B may reduce the risk of HCC but cannot be eliminated due to other factors that are not amenable to change by antiviral therapy.

This study aims to evaluate the treatment outcome of long term tenofovir disoproxil fumarate (TDF) in chronic hepatitis B patients in one of the tertiary centres in Malaysia. The proportion of chronic hepatitis B patients who achieved virological suppression at different time points will be determined. This study will also identify factors that influence the complete virological suppression in chronic hepatitis B patients treated with TDF. In addition to that, this study will demonstrate the association between complete virological suppression with clinical response (development of liver cirrhosis complications and hepatocellular carcinoma), biochemical response (normalisation of ALT), and survival rate of treated chronic hepatitis B patients.

CHAPTER 2: OBJECTIVES OF STUDY

Main Objective

To evaluate the treatment outcome of long-term tenofovir disoproxil fumarate (TDF) therapy in chronic hepatitis B patients in Hospital Sultanah Nur Zahirah.

Specific Objectives

1. To determine the proportion of chronic hepatitis B patients achieving complete virological suppression and partial virological suppression after being treated with TDF at 12 months and 24 months of therapy in Hospital Sultanah Nur Zahirah.
2. To identify factors associated with complete virological suppression in chronic hepatitis B patients treated with TDF in Hospital Sultanah Nur Zahirah.
3. To determine the association between complete virological suppression and clinical outcomes (development of variceal bleeding, ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, and hepatocellular carcinoma), biochemical response (normalisation of ALT), and survival rates at 12 months and 24 months of therapy in chronic hepatitis B patients treated in Hospital Sultanah Nur Zahirah.

CHAPTER 3: MANUSCRIPT

TITLE: Treatment outcome of Tenofovir Disoproxil Fumarate (TDF) Among Chronic Hepatitis B patients: A Retrospective Review in Hospital Sultanah Nur Zahirah

Author: Ahmad Wafiy WAMZAH[1],

Corresponding authors: Amry A. RAHIM[1], Syuhada Dan ADNAN[2], Ahmad Filza ISMAIL[3]

[1]Department of Internal Medicine, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia

[2]Department of Hepatology and Gastroenterology, Hospital Sultanah Nur Zahirah, 20400 Kuala Terengganu, Terengganu, Malaysia

[3]Department of Biostatistics, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia

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3.1 Abstract

Background: Tenofovir disoproxil fumarate (TDF) is among the high barrier nucleotide analogue currently preferred as first-line therapy in chronic hepatitis B patients. Its safety and efficacy have been confirmed in 2 phase III clinical trials. However, no reports have been published on the experience with TDF among Southeast Asian populations, including Malaysia. The objectives of the study are to determine the proportion of chronic hepatitis B patients achieving complete virological suppression after being treated with TDF at 12 months and 24 months of therapy in Hospital Sultanah Nur Zahirah and to identify factors associated with the complete virological suppression.

Methods: This was a retrospective cohort study using secondary data, which involved chronic hepatitis B patients treated with Tenofovir Disoproxil Fumarate (TDF) for at least 3 months, between 1st January 2017 and 31st December 2021. The proportion of chronic hepatitis B patients who achieved complete virological response (CVR) at the end of 12 and 24 months of therapy was evaluated. Additionally, the association of complete virological response with clinic demographic factors, clinical outcome (liver cirrhosis-related complications, development of hepatocellular carcinoma), biochemical response, and survival status was also analysed.

Result: 108 patients who fulfilled the inclusion criteria were identified. 60.5% (49 out of 81) patients achieved complete virological response at 12 months of TDF therapy, and 76 out of 90 (84.4%) patients achieved complete virological response at the end of 24 months of TDF therapy. Analysis using multiple logistic regression showed the presence of HBeAg antigen as the only factor associated significantly with complete virological suppression. (OR= 8.246, 95% CI: 2.093 – 32.487, p-value = 0.003). Using chi-square tests, the association of complete virological suppression at 24 months of TDF therapy was shown to be statistically significant (p-value < 0.001) with the reduction of liver cirrhosis complications, namely variceal bleeding,

ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, and incidence of hepatocellular carcinoma. The normalisation of ALT levels was shown to be significantly associated with complete virological suppression at 12 months and 24 months of TDF therapy.

Conclusion: Our experience from this study shows that TDF is an effective therapy for chronic hepatitis B patients in our population. Induction of long-term suppression of HBV DNA should be the primary endpoint of treating chronic Hepatitis B patients as this is significantly associated with favourable clinical outcomes, preventing further disease progression and development of hepatocellular carcinoma, thus improving overall survival.

Keywords: CVR, TDF, HBV DNA levels, liver cirrhosis, hepatocellular carcinoma

3.2 Introduction

Hepatitis B infection remains a global public health burden with significant morbidity and mortality. The World Health Organization (WHO) estimates that 296 million people were living with chronic hepatitis B infection in 2019, with an estimated 1.5 million new infections yearly. WHO also estimated that in 2019, hepatitis B resulted in 820 000 deaths, primarily due to complications from liver cirrhosis and hepatocellular carcinoma(1).

In Malaysia, up till 2017, 35 861 cases had been reported to the Ministry of Health (MOH). (2) According to the ministry report, 5% of the Malaysian population lives with hepatitis B (3). The incidence rate of hepatitis B also increased from 2.26 per 100,000 in 2010 to 12.65 per 100,000 in 2015 (2) and is projected to increase further between 2010 and 2040 (4).

Managing chronic hepatitis B patients is challenging due to the lack of direct effects of currently available therapies on the viruses' covalently closed circular DNA (cccDNA). Besides that, integrated HBV DNA into the host genome is another barrier that causes the Hepatitis B virus to be more challenging to eradicate. (16) The goals of treatment in managing chronic hepatitis B patients remain to improve survival by preventing progression to liver cirrhosis and the development of hepatocellular carcinoma(6). To achieve this, the European Association for the Study of the Liver (EASL) recommends the induction of long-term virological suppression of HBV DNA as the primary endpoint of the therapy (6).

Tenofovir disoproxil fumarate (TDF) is among the high barrier nucleotide analogue, which is currently preferred as first-line therapy in chronic hepatitis B patients. (level III evidence) (6) (17) (18). Its safety and efficacy have been confirmed in 2 phase III clinical trials. In a large, multi-centre randomised controlled trial (RCT), TDF was equally effective with ETV in HBV DNA suppression (p=0.807) and a comparable side effect profile among NA-naïve CHB

patients at long-term follow-up of 144 weeks (19). Rates of virological suppression at week 48 were 76% for HBeAg-positive patients and 93% for HBeAg-negative patients (20). In a more extended treatment duration at week 240, >98% of chronic hepatitis B patients who received TDF therapy achieved virological suppression despite a high pre-treatment baseline viral load (21).

There are limited data describing TDF's efficacy in the "real world" population. A few studies earlier describe populations in Europe, North America, Australia, and China. However, no reports have been published on the experience with TDF among Southeast Asian populations, including Malaysia. The rates of TDF response in the Malaysian population are unknown. This study aimed to evaluate the outcome of TDF therapy among chronic Hepatitis B patients in one of the tertiary centres in Malaysia.

3.3 Methodology

This was a retrospective cohort study using secondary data, which involved chronic hepatitis B patients treated with Tenofovir Disoproxil Fumarate (TDF) 300mg daily for at least 3 months, between 1st January 2017 and 31st December 2021 at Hospital Sultanah Nur Zahirah. The study population involved all the chronic hepatitis B patients who fulfilled the criteria. The inclusion criteria were older than 18 years old, diagnosed with chronic hepatitis B infection (based on 2018 AASLD Hepatitis B Guidance), and received Tenofovir Disoproxil Fumarate (TDF) 300mg daily for at least 3 months duration. The exclusion criteria were Hepatitis C or HIV co-infection, patients who had cancers or liver transplantation before or within the first 3 months of treatment, alcoholic liver disease, and autoimmune hepatitis.

Definitions of response

Complete virological response was defined as plasma HBV DNA level of < 20 IU/mL meanwhile partial virological response was defined as plasma HBV DNA level of ≥ 20 IU/mL but < 2000 IU/mL. (12)

Statistical Analysis

The data collected was analysed as a descriptive type of analysis. Statistical analysis was conducted using Statistical Package for the Social Sciences (SPSS) Ver 26.0. The categorical variables were described by frequency (n) and percentage (%). The numerical variable was described using mean (SD). Comparison between categorical variables was analysed using Chi-square tests or logistic regression. A p-value of < 0.05 will be considered significant. Survival analysis using the Kaplan-Meier survival was also conducted to determine influences

on the time to overall survival, development of decompensated liver cirrhosis-related conditions, and development of hepatocellular carcinoma.

Ethical issue

Ethical approval was obtained from Jawatankuasa Etika Penyelidikan (Manusia) – JEPeM, Universiti Sains Malaysia on 28th June 2022 with study protocol code USM/JEPeM/22030155 and National Medical Research Registry (NMMR) Malaysia on 20th June 2022 with NMMR ID-22-01165-10A (IIR).

3.4 Results

Clinico Demographic characteristics

From a total of 115 patients who were screened, 108 patients who fulfilled the inclusion and exclusion criteria were included in this study. 7 patients were excluded due to following reasons: 3 patients defaulted follow-up after 3 to 6 months of TDF therapy, 2 patients had diagnosis of carcinoma upon TDF initiation (1 patient had hepatocellular carcinoma and another patient had chronic myeloid leukaemia), 1 patient had concomitant hepatitis C co-infection, and another patient only started on TDF therapy for 3 months then changed to Entecavir due to unbearable side effects (dizziness, nausea and vomiting).

Their clinical, and demographic characteristics are summarised in Table 1. The majority of patients were male (74.1%), of Malay ethnicity (97.2%), and HBeAg negative disease (66.7%). 66 (61.1%) patients were treatment naïve, and 73 (67.6%) patients were non-cirrhotic upon commencement of the TDF therapy. 61 (56.5%) patients had HBV DNA levels > 2000 IU/ml before TDF therapy, of which 18 (29.5%) patients already had liver cirrhosis. 44 (40.8%) patients had HBV DNA baseline level < 2000 IU/ml at the initiation of TDF therapy. Most of them were treatment-experienced patients and had switched to TDF due to the unavailability of previous second-line nucleotide analogues.

Virological response

Virological response to TDF is detailed in Table 2 and Figure 1. Overall, 76 (84.4%) patients achieved complete virological response at the end of 24 months of TDF therapy. The rates of complete virological response were 38.5 % (5/13) at 3 months, 68.6 % (24/35) at 6 months, and 60.5% (49/81) at 12 months of TDF therapy. 87 out of 90 patients (96.6%) achieved at

least partial virological suppression (HBV DNA < 2000 IU/mL) at 24 months of TDF therapy. A total of five patients failed to maintain complete virological suppression throughout the follow-up, and 1 of them had transient virological breakthroughs. This was associated with a report of non-compliance. In that patient, HBV DNA levels rose from undetected (at baseline and 3 months of therapy) to 144 IU/ml at 12 months. However, after better compliance, that patient achieved complete virological suppression at 24 months of the TDF therapy.

Biochemical outcomes

Mean ALT at baseline was 157.2 IU/ml and 52.2 IU/ml after 24 months of TDF therapy. Decompensated liver cirrhosis patients had a lower mean baseline ALT than compensated liver cirrhosis patients and those patients without liver cirrhosis. (39.1 IU/ml *vs* 115.4 IU/ml *vs* 187.7 IU/ml). Non-liver cirrhotic patients have the highest mean change in ALT at the end of follow-up (-142.5 IU/ml), followed by compensated liver cirrhosis (-75.6 IU/ml) and decompensated liver cirrhosis patients (-8.8 IU/mL). Baseline serum ALT levels were in the normal range in 40/108 patients (37.0%). By the end of 24 months with TDF therapy, 62/102 (60.8%) patients had a normal range of ALT levels.

Associated factors with complete virological suppression

Figure 1 depicted fluctuation in partial virological suppression with different treatment time points, compared with complete virological suppression which was more consistent. Besides compliance issues, other factors which may contribute to such findings were decompensated liver cirrhosis status and the presence of Hbe antigen.

As described in Table 3, analysis from simple logistic regression showed age and the presence of HBeAg antigen as factors that have a significant association (p-value < 0.05) with complete virological suppression when other co-founders were not adjusted. Further analysis using multiple logistic regression showed the presence of HBeAg antigen as the only factor associated significantly with complete virological suppression. (OR= 8.246, 95% CI: 2.093 – 32.487, *p*-value = 0.003). (Table 4)

Clinical outcomes

Survival analysis of the clinical outcomes (development of liver cirrhosis-related complications: variceal bleeding, ascites, hepatic encephalopathy, hepatocellular carcinoma) and overall survival is presented in Figure 2. Hepatocellular carcinoma was diagnosed in 4 patients. The first patient was diagnosed within 6 months of TDF therapy, the second patient at 12 months of TDF therapy, meanwhile the remaining two patients were diagnosed at 24 months of TDF therapy. The first patient had compensated liver cirrhosis at baseline and died due to the malignancy at 12 months of follow-up. The second patient did not have liver cirrhosis at baseline but could not achieve at least partial virological suppression throughout the follow-up. The remaining two patients had liver cirrhosis before TDF therapy and failed to achieve at least partial virological suppression following the TDF therapy.

Association of complete virological suppression with clinical outcome, biochemical response, and survival status

Table 5 summarises the association of complete virological suppression with clinical outcome, biochemical response, and survival status of chronic hepatitis B patients. Using chi-square

tests, the association of complete virological suppression at 24 months of TDF therapy was shown to be statistically significant (p-value < 0.001) with the reduction of liver cirrhosis-related complications, namely variceal bleeding, ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, and incidence of hepatocellular carcinoma. The normalisation of ALT levels was shown to be significantly associated with complete virological suppression at 12 months and 24 months of TDF therapy. The association of overall survival with complete virological suppression at 24 months of TDF therapy was also significant.

Treatment safety

Our study also revealed no significant renal function decline with TDF therapy. Mean serum creatinine for our patients prior to TDF initiation was 71 µmol/L. After TDF initiation, mean serum creatinine were 81 µmol/L and 80 µmol/L; at 12 months and 24 months of the therapy respectively.

3.5 Discussion

Tenofovir disoproxil fumarate (TDF) is a high barrier nucleotide analogue recommended for first-line therapy in chronic hepatitis B patients. Based on clinical trials, it has been associated with high rates of virological suppression, thus preventing liver cirrhosis-related complications and hepatocellular carcinoma, thus improving overall survival. Post-registration real-world studies confirm the treatment efficacy outside the selected clinical trial situation. This study validates the effectiveness of TDF therapy in chronic hepatitis B patients treated in one of the tertiary centres in Malaysia.

The study population was predominantly male and HBeAg negative, similar to the clinical trials and most available real-life studies. 73.1 % of the study population were aged more than 40 years old. While clinical trials studied a predominantly Caucasian population, this study focused on the Asian population, mostly Malay. 38.9 % were treatment-experienced patients with other antiviral agents, and 32.4 % had liver cirrhosis before TDF therapy.

The efficacy of TDF therapy in our study population reflects the clinical trial experience. 76 (84.4%) chronic hepatitis B patients achieved complete virological suppression and 87 (96.6%) achieved at least partial virological suppression at the end of 24 months of TDF therapy. Over time, 95.3% of chronic hepatitis B patients maintained complete virological suppression. No resistance of TDF was detected in this study. A transient virological breakthrough was observed in one patient who was documented to be non-compliance. This reflects the importance of patient engagement strategies, including education and shared decision-making. Peer support groups may also contribute to better adherence and outcome.

Based on our study, the only variable independently associated with complete virological suppression is the HBeAg seropositivity. Our findings are in keeping with other “real-life” studies. In a study among the South Korean population by Sara Jeong et al., 127 out of 154

(82.5%) patients achieved complete virological suppression after 48 weeks of TDF administration (14). This finding is similar to another study conducted among the Australian population, in which 77 (83.7%) patients achieved complete virological suppression by the end of follow-up. In this same study, baseline HBV DNA levels and the presence of HBeAg were found to be significantly associated with complete virological suppression at the end of follow-up.

The European Association of the Study of the Liver (EASL) states that response to hepatitis B treatment can be divided into virological, serological, biochemical, and histological responses (22). In this study, we also evaluate the biochemical response, defined as the normalisation of ALT levels based on an upper limit of ~40 IU/ml. (11) Our chronic hepatitis B patients who received TDF therapy also had a mean ALT improvement from 157.2 IU/ml to 52.2 IU/ml, and the percentage of those who had normal ALT at baseline was 37.0%, which increased to 60.8% after 24 months of TDF therapy. The normalisation of ALT was also significantly associated with complete virological suppression at 12 months and 24 months of TDF therapy. This may support the use of ALT levels as surrogate markers for response in treated chronic hepatitis B patients, especially in resource-limited centres which have limited access to HBV DNA levels measurement.

Besides that, the complete virological response at 24 months of TDF therapy was found to be significantly associated with reduction of liver cirrhosis-related complications: variceal bleeding, ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, and incidence of hepatocellular carcinoma. Thus, this leads to improved overall survival in chronic hepatitis B patients, which is also statistically significant.

3.6 Conclusion, Study Limitation, and Recommendation

Our experience from this study shows that TDF is an effective therapy for chronic hepatitis B patients. The rate of complete virological suppression was high, and further study may evaluate the rate of sustained complete virological suppression with a longer duration of follow-up. The presence of HBeAg was associated with a slower time to complete virological suppression. In addition, induction of long-term suppression of HBV DNA should be the primary endpoint of treating chronic Hepatitis B patients as this is significantly associated with favourable clinical outcomes, preventing further disease progression and development of hepatocellular carcinoma, thus improving overall survival.

Our study has a few limitations. First is the small number of patients and involving only a single centre. A larger sample size and involving multiple centres may add to the strength of this study. Secondly, there were some reasons the HBV DNA levels could not be repeated due to limited resources and the unavailability of the reagents. Due to this reason, the decision on patient management will depend on clinical evaluation and other parameters, namely biochemical response (i.e., ALT normalisation). Thirdly is the compliance issue. Given the difficulty of eradicating the hepatitis B virus with the currently available treatment, patients must be motivated to comply, and most need to continue taking lifelong. In addition, future studies should also evaluate the safety of TDF therapy.

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3.8 Tables and Figures

Table 1: Baseline demographics in chronic hepatitis B patients who received TDF therapy

Baseline demographics	**Total population (n = 108)**	**Liver cirrhosis (n = 35)**		**Non–cirrhotic liver (n = 73)**
		Compensated (n = 25)	**Decompensated (n = 10)**	
Age (year)	49 (23 – 75)	54 (34 – 75)	60 (53 -71)	47 (23 -75)
Gender *n* (%)				
Male	80 (74.1)	15 (60.0)	10 (100.0)	29 (61.7)
Female	28 (25.9)	10 (40.0)	0 (0.0)	18 (38.3)
Ethnics *n* (%)				
Malay	105 (97.2)	25 (100.0)	10 (100.0)	70 (95.9)
Chinese	3 (2.8)	0 (0.0)	0 (0.0)	3 (4.1)
Hbe Ag status *n* (%)				
Hbe Ag positive	36 (33.3)	10 (40.0)	1 (10.0)	25 (34.2)
Hbe Ag negative	72 (66.7)	15 (60.0)	9 (90.0)	48 (65.8)
Treatment history *n* (%)				
Experienced	42 (38.9)	12 (48.0)	3 (30.0)	27 (37.0)
Lamivudine	15 (35.7)	2 (16.6)	3 (100.0)	10 (37.0)
Telbivudine	7 (16.7)	3 (25.0)	0 (0.0)	4 (14.8)
Entecavir	9 (21.4)	2 (16.7)	0 (0.0)	7 (25.9)
Adefovir/Lamivudine*	2 (4.8)	0 (0.0)	0 (0.0)	2 (7.4)
Lamivudine/Entecavir*	7 (16.7)	4 (33.3)	0 (0.0)	3 (11.1)
Lamivudine/Telbivudine*	1 (2.4)	1 (8.3)	0 (0.0)	0 (0.0)
Entecavir/Telbivudine*	1 (2.4)	0 (0.0)	0 (0.0)	1 (3.7)
Naïve	66 (61.1)	13 (52.0)	7 (70.0)	46 (63.0)

Baseline demographics (*continued..)*	**Total population (n = 108)**	**Liver cirrhosis (n = 35)**		**Non–cirrhotic liver (n = 73)**
		Compensated (n = 25)	**Decompensated (n = 10)**	
Co-morbid *n* (%)				
Diabetes Mellitus	20 (18.5)	6 (24.0)	4 (40.0)	10 (13.7)
Hypertension	19 (17.6)	5 (20.0)	1 (10.0)	13 (17.8)
Dyslipidemia	32 (29.6)	5 (20.0)	4 (40.0)	23 (31.5)
HBV DNA load (IU/ml) *n* (%)				
< 20	22 (20.4)	5 (20.0)	2 (20.0)	15 (20.5)
21 -2000	22 (20.4)	6 (24.0)	2 (20.0)	14 (19.2)
2001 – 200000	26 (24.1)	2 (8.0)	4 (40.0)	20 (27.4)
>200000	35 (32.4)	11 (44.0)	1 (10.0)	23 (31.5)
not available	3 (2.8)	1 (4.0)	1 (10.0)	1 (1.4)
ALT (IU/mL) *n* (%)				
0 – 20	16 (14.8)	3 (12.0)	2 (20.0)	11 (15.0)
21 – 40	24 (22.2)	6 (24.0)	3 (30.0)	15 (20.6)
41 – 400	62 (57.4)	15 (60.0)	5 (50.0)	42 (57.5)
>400	6 (5.6)	1 (4.0)	0 (0.0)	5 (6.9)

*Previous treatments were given in sequential

Table 2: Virological suppression at on-treatment time points (n=108).

Follow-up (months)	0	3	6	12	24
Patients with viral load *n* (%)	105 (97.2)	13 (12.0)	35 (32.4)	81 (75.0)	90 (83.3)
Complete Virological suppression (HBV DNA <20 IU/mL) *n* (%)	22 (21.0)	5 (38.5)	24 (68.6)	49 (60.5)	76 (84.4)
Partial Virological suppression (HBV DNA 20-2000 IU/mL) *n* (%)	22 (21.0)	6 (46.2)	9 (25.7)	26 (32.1)	11 (12.2)

***** "Patients with viral load" refers to the number of patients at each time point who had available HBV DNA reading