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ORIGINAL ARTICLE

Two-year Single-Center Real-Life Data of Tenofovir Disoproxil Fumarate Treatment for Chronic Hepatitis B Patients in Taiwan

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ABSTRACT

AIM: Chronic infection with hepatitis B virus (CHB) is a worldwide disease. The aim of this study was to evaluate the treatment efficacy and renal tolerability of Tenofovir disoproxil fumarate (TDF) in patients with CHB.
METHODS: Data from patients were retrospectively collected from January 2012 to September 2014. The inclusion criteria included CHB, high serum HBV DNA, high serum alanine aminotransferase (ALT), and persistent use of TDF for at least one year. The exclusion criteria included HCV or HIV coinfection. The therapeutic efficacy was recorded at screening and every 6 months thereafter.
RESULTS: Among all 100 enrolled subjects, 28 and 24 patients were HBe-positive and treatment-experienced, respectively. The 2-year biochemical response (ALT less than 40 U/L) was 95% to 100%, virologic response (HBV DNA < 20 IU/mL) was 86% to 98%, and serologic response (HBeAg seroloss) was 33%. No cases with HBsAg clearance were detectable. No significant difference existed between treatment-naïve and -experienced patients, but those with positive HBe had a poor virological response compared with the negative HBe group ($P = 0.043$). There was no significant change in renal function.
CONCLUSION: TDF treatment was considered as a efficient, safe and well tolerated therapy to CHB individuals.

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Key Word: Hepatitis B; Tenofovir

BACKGROUND

Chronic infection with hepatitis B virus (HBV) results in substantial morbidity and mortality worldwide. It is estimated that 400 million people worldwide are affected by chronic Hepatitis B (CHB) infection[1]. Persistent HBV replication with active hepatitis leads to disease progression, including cirrhosis, liver failure, and hepatocellular carcinoma (HCC)[2]. Treatments that suppress viral replication forestall disease progression[3]. Oral antivirals can effectively suppress viral replication. Tenofovir disoproxil fumarate (TDF), the oral prodrug of tenofovir, is a nucleotide analogue with potent activity against HBV DNA polymerase. The agent was approved by the US Food and Drug Administration (FDA) for the firstline treatment of CHB on the basis of acceptable Phase III clinical study results. Furthermore, current guidelines recommend

Table 1 Baseline characteristics of enrolled subjects.		
		N = 100
Mean follow-up times (months)		21.2 (12-24)
Median Age (years)		51.1 (19-78)
Male (%)		65 (65%)
HBeAg status (%)	HBeAg+	28 (28%)
	HBeAg-	72 (72%)
HBV genotype	B	74 (74%)
	C	26 (26%)
Treatment naïve (%)		76 (76%)
Mean HBV DNA (IU/mL)	HBeAg+	9.1×10^7
	HBeAg-	1.5×10^7
Mean ALT (U/L)		357.4 (50-3378)
Cirrhosis (%)		13 (13%)
HCC (%)		10 (10%)

	Week 24		Week 48		Week 72		Week 96	
	e+	e-	e+	e-	e+	e-	e+	e-
ALT ≥ 40 U/L	11	24	4	11	3	4	0	2
ALT < 40 U/L	17	48	24	61	19	64	21	48

Figure 1 The biochemical responses between HBe-positive and -negative patients.

	Week 24		Week 48		Week 72		Week 96	
	TN	TE	TN	TE	TN	TE	TN	TE
ALT ≥ 40 U/L	25	14	10	5	6	1	1	1
ALT < 40 U/L	51	10	66	19	53	19	49	19

Figure 2 The virologic responses between HBe-positive and -negative patients.

that the most potent drugs with optimal resistance profiles, such as TDF and entecavir (ETV) should be used as firstline monotherapies in CHB[4,5]. However, nephrotoxicity may be a potential concern with TDF, based on evidence from postmarketing surveillance of patients receiving TDF for human immunodeficiency virus (HIV) infection[6]. Therefore, accumulating data from observational real-life cohort studies have added considerably to our understanding of the efficacy and safety profiles of TDF. The aim of this study was to evaluate the treatment efficacy and renal tolerability of TDF in a Chinese population with CHB infection.

MATERIALS AND METHODS

Data from patients at Taichung Veterans General Hospital were retrospectively collected from January 2012 to September 2014. The enrolled individuals had been diagnosed with CHB (defined as a positive serum hepatitis B surface antigen (HBsAg) test for at least 6 months), high serum HBV DNA (> 20000 IU/ml in HBe-positive cases and > 20000 IU/ml in HBe-negative ones), high serum alanine aminotransferase (ALT) at screening (> 2-fold upper normal limit. The definition of upper normal limit of ALT was 50 U/L in men and 35 U/L in women), and had persistently taken TDF for at least one year. The exclusion criteria included hepatitis C virus (HCV) or HIV coinfection. These cases were further classified according to the presentation of hepatitis B e antigen (HBeAg) (HBe-positive and -negative), and prior treatment history (treatment-naïve and -experienced). The therapeutic efficacy, including serum ALT, HBV DNA levels, and the portion of patients with HBeAg or HBsAg loss, were recorded at screening and every 24 weeks (6 months) thereafter. The biochemical, virological, and serological responses were defined as serum ALT < 40 U/L, HBV DNA < 20 IU/ml and HbeAg loss, respectively. The renal function and serum creatine level were also recorded at the next follow-up visit of each subject.

The method of HBV DNA quantification in our study is using real-time PCR (Cobas AmpliPrep/Cobas TaqMan HBV Test). Data including gender, positive ratio of HBe-positive or negative, treatment naïve status, and concurrent cirrhosis or HCC at screening are expressed as percentages of the total patient number. Statistical comparisons were made using Pearson's chi-square test to compare the positive ratio of therapeutic responses of each group. Independent *t* test was used to analyze the changes in serum creatinine level. A *P*-value below 0.05 was considered statistically significant.

RESULTS

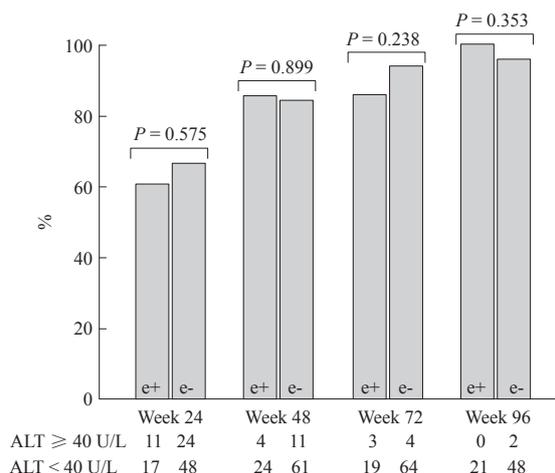From January 2012 to September 2014, 100 subjects were enrolled
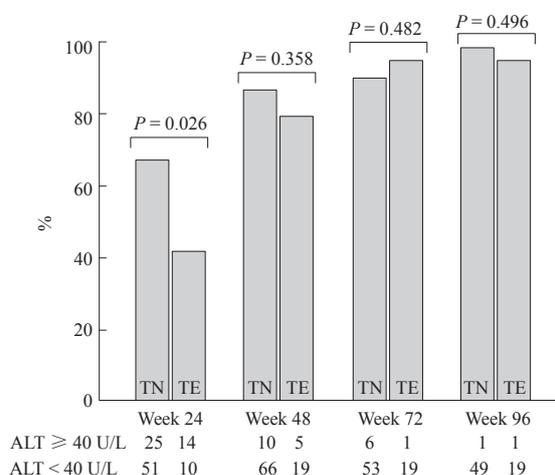
in this study. The characterisics of these cases are listed in Table 1. The mean age of these individuals was 51.1 years old, and male predominance (65%) was noted. Among these patients, 28 cases were Hbe-positive, and 72 were HBe-negative. There were 74 and 26 subjects belonged to HBV genotype B and C respectively. Furthermore, 76 and 24 patients were treatment-naïve and -experienced, respectively. Among the 24 treatment-experienced subjects, there were 5, 11, 7 and 1 cases having previous treatments with lamivudine, entecavir, telbivudine, and pegylated interferon respectively. The mean HBV DNA level was higher in the HBe-positive patients (mean HBV DNA 9.1×10^7 IU/mL) than in the HBeAg-negative patients (mean HBV DNA 1.5×10^7 IU/mL). There were 13 and 10 cases with cirrhotic liver and HCC at screening, which diagnosed with typical ultrasound or computed tomography (CT) images.

The biochemical responses between HBe-positive and -negative cases, or between prior treatment-naïve and -experienced cases, are displayed in Figures 1 and 2, respectively. The ratio of biochemical response at 48 weeks was 85.7% in HBe-positive patients, 84.7% in HBe-negative patients, 86.8% in treatment-naïve patients, and 79.2% in treatment-experienced patients. At 96 weeks, 100%, 96%, 98%, and 95% of the biochemical reponse rate was noted in HBe-positive, -negative, treatment-naïve, and -experienced cases,
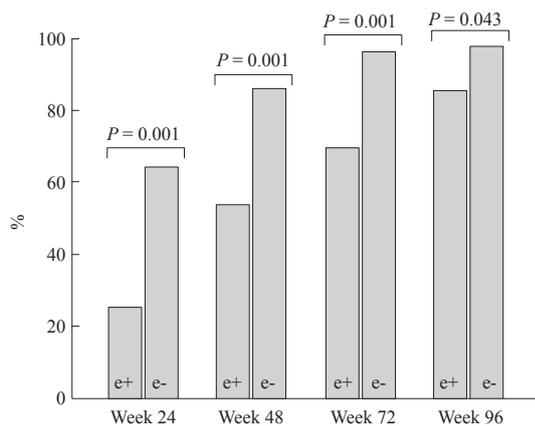
Fugure 3 The biochemical responses between treatment-naïve and-experienced patients.
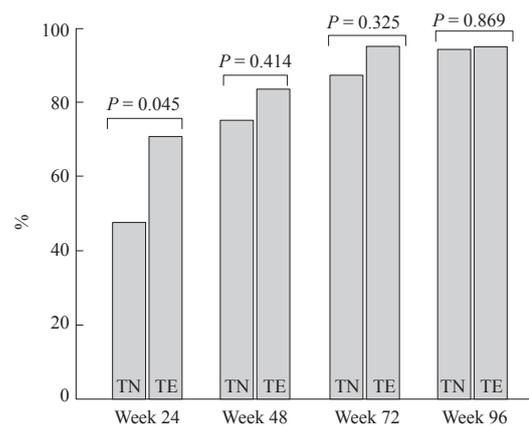
HBV
DNA ≥ 20 IU/mL 21 26   13 10   7 2   3 1
DNA < 20 IU/mL 7 46   15 62   16 56   18 48

Figure 4 The virologic responses between treatment-naïve and -experienced patients.

HBV
DNA ≥ 20 IU/mL 40 7   19 4   8 1   3 1
DNA < 20 IU/mL 36 17   57 20   54 19   47 19

e positive   21 6   18 6   15 5   5 5
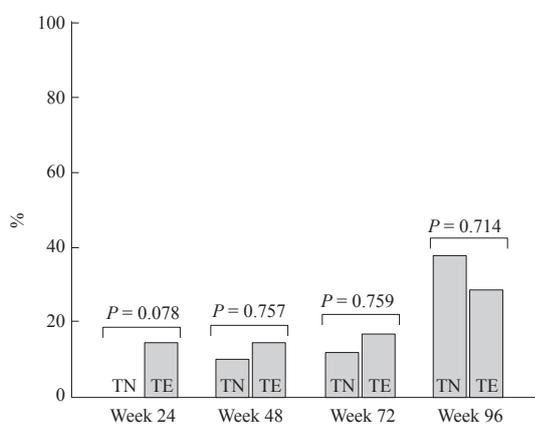e seroloss   0 1   2 1   2 1   3 2

Figure 5 The serologic responses between treatment-naïve and -experienced patients.
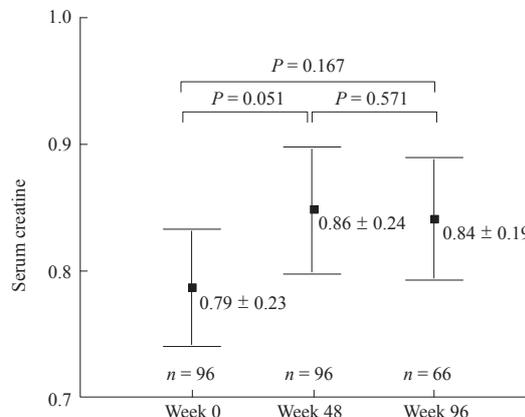

Figure 6 The change of renal function of individusals underwent TDF.

respectively. There were no significant differences among these groups.

The virological responses are shown in Figures 3 and 4, respectively. The rate of virological response at 48 weeks was 53.6% in HBe-positive patients, 86.1% in HBe-negative patients, 75% in treatment-naïve patients, and 83.3% in treatment-experienced patients. The overall virological response after 48 weeks of TDF treatment was 77%. At 96 weeks, 85.7%, 97.9%, 94%, and 95% of the virological response rates were noted in HBe-positive, -negative, treatment-naïve, and -experienced cases, respectively. The overall virological response at 96 weeks was 96%. There were no differences between treatment-naïve and -experienced cases, but the individuals with positive HBe had a significantly lower virological reponese rate than those with negative HBe ($P = 0.001$ at 48 weeks, $P = 0.043$ at 96 weeks).

The serological response among the HBe-positve subjects is displayed in Figure 5. There were 3 patients (11.1%) who achieved HBeAg loss at 48 weeks, and 5 cases (33.3%) at 96 weeks. There were no differences between cases with prior treatment and those without. No HBsAg clearance was detectable among all enrolled cases in our study.

The date of renal function of our patients is shown in Figure 6. The level of serum creatine level was 0.79 ± 0.23 mg/dL at

baseline, 0.86 ± 0.24 mg/dL at 48 weeks, and 0.84 ± 0.19 mg/dL at 96 weeks. No additional dosage adjustment or cessation of TDF was needed. There was no significant change of renal function.

DISCUSSION

In our study with 100 enrolled subjects, the 2-year biochemical response was 95% to 100%, virologic response was 86% to 98%, and serologic response was 33%. No significant difference existed between treatment-naïve and -experienced patients, and there was no significant change in renal function.

CHB is a major global health problem, and the goal of CHB treatment is to reduce viral replication, subsequent liver inflammation and fibrosis, and risk of developing cirrhosis and HCC.[1] The currently available antiviral treatment for CHB can be divided into two classes of therapeutic agents: nucleos(t)ide analogue (NUC), including lamivudine (LAM), telbivudine, entecavir, adefovir, tenofovir, and interferon (IFN)/pegylated interferon (PEG-IFN). The advantage of treatment with IFN/PEG-IFN is its predefined therapeutic period, but NUCs are more popular therapeutic agents based on clinical indication. Among the several NUCs available, potent antivirals without the propensity to select for resistance are desirable.

TDF is the oral prodrug of tenofovir, with antiviral activities against HBV and HIV. The first multicenter phase III trials, studies 102 (HBe-positve patients) and 103 (HBe-negative patients), were

Table 2 Summary of cohort studies on therapeutic efficacy of TDF.

	Study 103 (7-9)	Study 102 (7,9)	King's College Cohort (10)	European Cohort (11)	United states Cohort (12)	German Cohort (13)	Our Cohort
Baseline characteristics							
N	176	250	60	302	28	184	100
Mean age (years)	34	44	40	55	36	44	51.1
Male (%)	68%	77%	50%	74%	58%	69%	65%
HBeAg + (%)	100%	0%	33%	20%	100%	31%	28%
Treatment naïve (%)			100%	100%	100%	46%	76%
Cirrhosis (%)	20%	19%	23%	35%	NR	11%	13%
Treatment efficacy							
Median follow-op (years)	Ongoing	Ongoing	1	2.7	1	2	1.76
Virological response							
Cutt-off (IU/mL)	69	69	60	12	100	69	20
Year 1	76%	93%	76%	84% (HBe+ 66%, HBe- 74%)	82%	NR	77% (HB+ 53.6%, HBe- 86.1%)
Year 2	78%	NR	X	95% (HB+ 86%, HB-98%)	X	92%	96% (HB+ 85.7%, HB- 97.9%)
Year 3	87%	72%	X	NR	X	X	X
Serological response							
Year 1	NR	X	7%	NR	5%	NR	11.10%
Year 2	22.20%	X	X	NR	X	20%	33.30%
Year 3	34%	X	X	36%	X	X	X
HBsAg loss (N)	8%	NR	0	13% in HBe+	0	5% in HBe+	0

designed to continue assessing the safety and efficacy of TDF treatment[7-9]. After 48 weeks of TDF treatment, HBV DNA was less than 69 IU/ml in 93% of HBe-negative and in 76% of HBe-positive patients. No difference was found between patients previously treated with lamivudine and those that had not received this drug. The rate of HBeAg loss was 21%, and HBsAg was lost in five patients[7]. Further follow-up of HBe-negative cases for 96 weeks showed that TDF treatment was able to maintain suppressed HBV DNA levels in 78% of patients. The cumulative HBeAg seroconversion was 22.2%[8]. At week 144, 87% of HBe-positive and 72% of HBe-negative patients had levels of HBV DNA less than 69 IU/ml. Moreover, 34% had lost HBeAg, and 8% of HBeAg-positive patients also lost HBsAg. Resistance to tenofovir was not detected in any patient[9]. Longer treatment with TDF was associated with greater HBV DNA negativization rates (98%-99%)[10]. Furthermore, in one prospective study including 641 patients, up to 5 years of treatment with TDF can lead to regression of hepatic fibrosis and cirrhosis[11].

There have been a few real-life cohort studies on the therapeutic efficacy of TDF. One single-center cohort study, the King's College Cohort, included 60 patients receiving firstline TDF treatment. HBeAg seroconversion over 12 months was reported in 7% of patients and no patients cleared HBsAg[12]. Another multicenter cohort study, the European cohort, conducted at 19 European centers, retrospectively and prospectively monitored 302 consecutive NUC-naïve patients with CHB who received TDF for a median of 28 months. HBeAg seroconversion was seen in 11 patients and HBsAg loss was seen in seven patients. No potentially resistance-associated mutations have been identified to date[13]. In a study in the United States which enrolled 333 consecutive treatment-naïve CHB patients for up to 12 months, twenty-eight of them received treatment with TDF. Furthermore, 82% of TDF-treated patients cleared HBV DNA, 5% achieved HBeAg seroconversion, and no patient cleared HBsAg[14]. Another prospective observational study that included 400 TDF-naïve patients was performed in Germany and the 2-year data are available (GEMINIS study). Overall, 92% of patients achieved undetectable levels of HBV DNA, 20% achieved HBeAg seroconversion, and there was 5% loss in HBsAg in HBe-positive patients[15].

The results of the above phase III/cohort studies and our study are summarized in Table 2. During the follow-up period in our enrolled cases, the 48-week overall biochemical response rate was 95% to 100%, the virologic response rate was 86% to 98%, and the serologic response rate was 33%. Unsurprisingly, the virologic reponse was significantly worse in HBe-positive cases than in HBe-negative cases in the initial period, which was similar to the results of previous studies[7,9,12,14]. A possible reasons for this phenomenon may be that HBe-positive cases usually have a higher HBV DNA viral load, so a longer theraepuetic time tends to be needed to achieve an undetectable level. No subjects with HBsAg loss was noted in our study, and this might have been due to the relatively short observation period (mean follow-up time, 1.76 years), and a prolonged follow-up period is needed to confirm this result.

Our result found similar responses between treatment-naïve and-experienced cases. A recently published study on long-term TDF treatment found no resistance detectable throughout a 7-year period[16]. Real-life studies have proven TDF retains significant activity against HBV virus in pretreated subjects with resistance to LAM, adefovir, or entecavir[17,18]. Our findings demonstrate that TDF provides a reasonable treatment modality not only for treatment-naïve HBV patients, but also for rescuing treatment-experienced cases with a high rate of genotypic resistance.

As previously mentioned, studies on HIV patients receiving TDF warn of the possiblity of renal function deterioration, but so far the problem appears to be less evident in HBV cases. The subjects in Study 103 had stable creatinine clearance rates over 4 years, and less than 1% of patients had confirmed increases in creatinine level of 0.5 mg/dL[19]. One prospective cohort study in France, the VIREAL study, evaluated the renal tolerance of HBV patients who underwent TDF and found stable glomerular filtration rate (GFR) in both elderly and younger cases[20]. Other real-life cohort studies also had a similar finding[12,14]. The creatinine level of our patients showed a slight increase at 48 weeks (mean 0.86 mg/dL) from baseline (mean 0.79 mg/dL), and then a decrease at 96 weeks (mean 0.84 mg/dL), meaning damage of renal function from TDF was temporal and not life-threatening. The baseline serum creatinine level of our enrolled cases was normal, and our result support that TDF was safe when used in the individuals without baseline renal impairment. The outcome of TDF use in subjects with renal impairment was not determinted and should need further investigation.

There were some limitations in our study. First, this was a real-life observational study and so was not retrospective in nature. Thus there was a lack of a standardized management protocol, and heterogeneity of the enrolled patients. Second, our study design included a relatively small number of cases and a short follow-up period. Last, the early markers of renal impairment, including creatinine clearence, serum phosphorus, urine glucose and urinary protein, were not recorded in our study. Further long-term research in representative samples of the general population are needed to confirm these results.

CONCLUSION

TDF treatment was shown to be an efficient, safe, and well-tolerated therapy for both treatment-naïve and -experienced CHB patients. HBe-positive subjects had a delayed virological response to TDF.

CONFLICT OF INTERESTS

The authors declare that they do not have conflict of interests.

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