Research Article ISSN 2639-9334

Gastroenterology, Hepatology & Digestive Disorders

Switchover to Tenofovir Disoproxil in Chronic HBV Patients with Primary Treatment Failure to Entecavir

Chee K Hui[1,2,3]* and Kit Hui[3]

[1]*Peter MacCallum Cancer Centre, Melbourne, Australia.*

[2]*Royal Melbourne Hospital, Melbourne, Australia.*

[3]*Department of Gastroenterology, Center for Digestive Diseases, Kuala Lumpur, Wilayah Persekutuan, Malaysia.*

***Correspondence:**
Chee K Hui., 31 Jalan Dua, 68000 Ampang, Kuala Lumpur, Wilayah Persekutuan, Malaysia.

Received: 15 Jul 2023; **Accepted:** 19 Aug 2023; **Published:** 26 Aug 2023

Citation: Chee K Hui, Kit Hui. Switchover to Tenofovir Disoproxil in Chronic HBV Patients with Primary Treatment Failure to Entecavir. Gastroint Hepatol Dig Dis. 2023; 6(1): 1-4.

ABSTRACT

Background/Aim: *Primary treatment failure to entecavir is known to occur in chronic hepatitis B virus (HBV) infection. Although the prevalence is low, the optimal management of this select group is unknown. This study aimed to determine the efficacy of tenofovir disoproxil in those with primary treatment failure to entecavir.*

Methods: *This study included 14 patients with primary treatment failure to entecavir. They were switched over the tenofovir disoproxil for 48 weeks.*

Results: *All 14 patients (100%) had reduction in serum HBV DNA by more than 2 $\log_{10}$ IU/ml at week 12 after tenofovir disoproxil treatment. All 14 patients (100%) still had elevated alanine aminotransaminase (ALT) levels at the time they were switched over to tenofovir disoproxil. At week 48 of tenofovir disoproxil, normalization of serum ALT levels occurred in 12 of these 14 patients (85.7%), and, 10 of the 14 patients (71.4%) had achieved both undetectable serum HBV DNA and normalization of serum ALT levels.*

Conclusion: *Tenofovir disoproxil is a safe and effective choice for the treatment of chronic HBV patients with primary treatment failure to entecavir treatment.*

Keywords

Chronic HBV, Primary treatment failure, Entecavir, Switchover, Tenofovir disoproxil.

Abbreviations

HBV: Hepatitis B virus; PTF: Primary treatment failure; ALT: Alanine aminotransaminase; HBeAg: Hepatitis B e antigen; HBsAg: Hepatitis B surface antigen; HCC: Hepatocellular carcinoma.

Introduction

Chronic hepatitis B virus (HBV) infection accounts for 500,000 to 1.2 million deaths each year and is the tenth leading cause of deaths each year [1]. Approximately 15-40% of chronic HBV patients will develop cirrhosis, liver failure or hepatocellular carcinoma (HCC) [1]. There is increasing evidence suggesting that persistent viral replication is an independent factor associated with the development of liver cirrhosis and HCC [2,3]. Thus, suppression of viral replication is an important in the management of these patients.

As the course of chronic HBV is typically silent until the development of HBV related complications such as liver cirrhosis or HCC, the major goal of treatment is the long-term prevention of these complications [4,5]. However, as these endpoints only occurs after decades of infection, phase III trials on treatment

of chronic HBV infection have used surrogate outcomes such as biochemical, virological and histological responses as well as hepatitis B e antigen (HBeAg) seroconversion and sustained virological response to assess the effectiveness of treatment. At the moment, eight agents, consisting of immunomodulators and nucleoside/nucleotide analogues, have been licensed for the treatment of chronic HBV and more are likely to be available in the future [5,6].

The six approved nucleoside/nucleotide analogues, lamivudine, adefovir dipivoxil, entecavir, tenofovir disoproxil, tenofovir alafenamide and telbivudine, can all result in reduction of HBV DNA, serum alanine aminotransaminase (ALT) levels and improvement in liver histology [5,6]. Unfortunately, the development of drug resistance is a factor associated with loss of efficacy [5,6].

While there have been many work and research published on the management or treatment of drug resistance mutations, little attention has been paid to a special subgroup of patients failing nucleoside/nucleotide analogues treatment for other reasons besides the emergence of drug resistance mutations.

These so called "primary treatment failure" has been defined by the American Association for the Study of Liver Diseases as a less than 2 $\log_{10}$ decrease in HBV DNA after 24 weeks of period of treatment and a less than 1 log10 drop in HBV DNA after 12 weeks of treatment by the European Association for the Study of Liver Diseases [7-9]. Therefore, the aim of this study is to investigate the effectiveness of tenofovir disoproxil in chronic HBV infected patients with primary treatment failure to entecavir.

Patients and Methods

Patients

A cohort of 876 patients followed at the Centre for Digestive Diseases, Kuala Lumpur, Malaysia from January 2010 to March 2021 was started on entecavir for treatment of chronic HBV infection. All the patients in this cohort fulfilled the following inclusion criteria: 1) hepatitis B surface antigen (HBsAg) positive for more than 6 months; 2) HBeAg positive or negative; 3) serum HBV DNA more than 4 $\log_{10}$ IU/ml; 4) serum ALT level above the upper limit of normal (7-33 U/L for women and 7-53 U/L for men respectively); 5) treatment naïve; and 6) absence of co-infection with hepatitis C virus, human immunodeficiency virus or hepatitis D virus.

Fourteen of these 876 patients (1.6%) were considered as primary treatment failure. These 14 patients (100%) had their entecavir stopped and were switched over to tenofovir disoproxil 300 mg daily (Gilead Science, Foster City, CA, USA) at 24 weeks after commencement of entecavir. This time point will be referred to as time of primary treatment failure.

Definition of Endpoints

Patients with a less than 2 $\log_{10}$ reduction of serum HBV DNA 24 weeks after commencement of entecavir was defined as primary treatment failure. HBeAg seroconversion was defined as loss of HBeAg accompanied by the development of anti-HBe for 2 consecutive readings three months apart.

Follow-Up Visits

All patients underwent a physical examination and blood testing for liver biochemistry [ALT, aspartate aminotransaminase, alkaline phosphatase, gamma-glutamyl transpeptidase, albumin and bilirubin], complete blood count, prothrombin time, activated partial thromboplastin time, urea, creatinine and electrolyte before commencement of entecavir. Liver biochemistry, complete blood count, HBV DNA, HBsAg, HBeAg and hepatitis B e antibody (anti-HBe) were also repeated on each follow-up.

All patients were followed-up every 4 weekly until end of follow-up. The end of follow-up was at 48 weeks after switching over to tenofovir disoproxil.

Virological Study

Serum HBV DNA was quantified by the Abbott real time HBV assay (Abbott Laboratories, Abbott Park, Ill, USA) with a linear range of 10-10^9 IU/ml. All 14 patients (100%) were screened for evidence of lamivudine, telbivudine, adefovir dipivoxil, tenofovir or entecavir resistance with the INNO-LiPA HBV Multi-DR kit (Fujirebio, Gent, Belgium) before switching to tenofovir disoproxil [10-13]. Patients with detectable serum HBV DNA were screened for tenofovir resistance at the end of follow-up.

Serum was tested for HBsAg, HBeAg and anti-HBe with enzyme linked immunosorbent assay (ELISA) (Abbott Laboratories, Chicago, Ill, USA). Anti-HCV, hepatitis D and HIV virus were tested by commercially available ELISA (Abbott GmBH Diagnostika, Wiesbaden-Delkenheim, Germany).

This study was approved by the local Institutional Review Board.

Statistical analysis

All statistical analyses were performed using the SPSS software (IBM SPSS Statistics for Windows, Version 20.0, IBM Corp, Armonk, New York, USA). The Mann-Whitney U test was used for comparing two continuous variables and the chi-square with Yates' correction for continuity or Fisher's exact test was used for comparing two categorical variables. Continuous variables were expressed as median (range). All p-values were 2-tailed, and p-values less than 0.05 were considered to be significant throughout this study.

Results

Patient Population

The baseline demographics between the responders and primary treatment failure before commencement of treatment with entecavir are shown in Table 1. There was no significant difference in the baseline demographics between the two groups (all p=NS).

Table 1: Baseline demographics before commencement of entecavir in those with primary treatment failure and those with response to entecavir.

	Primary Treatment Failure (n=14)	Responders (n=876)	P-value
Age, Years	50 (28-66)	46 (28-61)	0.43
Sex, Male: Female	8:6	510:366	0.94
Serum alanine aminotransaminase, U/L	245 (48-465)	294 (51-453)	0.25
Serum HBV DNA (Log_{10} IU/ml)	6.08 (5.32-8.24)	6.03 (6.00-8.42)	0.47
Hepatitis B e antigen status:			0.46
Positive	7	353	
Negative	7	523	
Hepatitis B antibody status:			0.46
Positive	7	523	
Negative	7	352	

The demographics of the 14 patients with primary treatment failure at time of primary treatment failure are shown in Table 2. No patient with primary treatment failure had developed either lamivudine, telbivudine, adefovir dipivoxil or entecavir resistance at the time they were switched over to tenofovir disoproxil treatment.

Table 2: Demographics of the 14 patients with primary treatment failure at the time of switch over to tenofovir disoproxil.

	Primary Treatment Failure (n=14)
Serum alanine aminotransaminase, U/L	90 (55-103)
Serum HBV DNA (Log_{10} IU/ml)	5.74 (3.82-7.98)
Hepatitis B e antigen status:	
Positive	7
Negative	7
Hepatitis B antibody status:	
Positive	7
Negative	7

Viral Suppression after Switched Over to Tenofovir Disoproxil

All 14 patients (100%) had reduction in serum HBV DNA by more than 2 log_{10} IU/ml at week 12 after tenofovir disoproxil treatment (Figure 1). The median HBV DNA at the end of follow-up was 1.00 (range <1.00- 3.16) log_{10} IU/ml.

Ten of the 14 patients (71.4%) had undetectable serum HBV DNA at the end of follow-up (48 weeks after switched over to tenofovir disoproxil).

Normalization of Serum ALT after Switched Over to Tenofovir Disoproxil

All 14 patients (100%) still had elevated ALT levels at the time they were switched over to tenofovir disoproxil. The serum ALT level is shown in Figure 1.

At week 48 of tenofovir disoproxil, normalization of serum ALT levels occurred in 12 of these 14 patients (85.7%).

Undetectable Serum HBV DNA and Normalization of Serum ALT Levels

At week 48, 10 of the 14 patients (71.4%) had achieved both undetectable serum HBV DNA and normalization of serum ALT levels.

HBeAg Seroconversion

Seven of these 14 patients were HBeAg positive at the time of primary treatment failure (Table 2). Two of these 7 patients (28.6%) developed HBeAg seroconversion after 8 and 36 weeks of tenofovir disoproxil respectively.

Side Effects and Tolerability

All 14 patients tolerated tenofovir disoproxil and none of these patients (0%) discontinued the drug. None of the 14 patients (0%) had developed any side effects to tenofovir disoproxil and none of these 14 patients (0%) had a more than 5.0% increase in serum creatinine level.

Tenofovir Resistance at the End of Follow-up

None of the 14 patients (0%) had evidence of tenofovir resistance at the end of follow-up.

Discussion

All six nucleoside/nucleotide analogues currently approved as first line treatment of chronic HBV infection has been demonstrated to be effective for the treatment of chronic HBV infection [4-6]. Despite the increasing potency of newer anti-HBV agents, there still exist a proportion of chronic HBV patients who will fail nucleoside/nucleotide analogue treatment. Recently, a distinction has been made in patients who fail treatment due to the emergence of drug resistant mutants or those with primary treatment failure [7-9].

Many chronic HBV patients do not achieve complete suppression of serum HBV DNA levels during treatment with nucleoside/nucleotide analogues. Factors that may contribute to primary treatment failure ranges from non-compliance to medications, inefficient conversion from the prodrug to its active metabolite, inadequate phosphorylation within the hepatocytes, genotypic dependent polymorphism or under dosing of the nucleoside/nucleotide analogues [14,15].

As both viral factors and host factors contribute to treatment outcomes or lack of treatment outcomes, it is difficult to assess the best treatment option for chronic HBV patients with primary treatment failure. Theoretically, all other nucleoside/nucleotide analogues should be effective. However, there has been very little clinical data on this topic. If we assume that randomization in all phase III clinical trials has led to an equal distribution of both viral and host factors, we would expect that drugs with more potent anti-viral activity may be able to suppress viral replication in these chronic HBV patients with primary treatment failure.

As in the United States, six nucleoside/nucleotide analogues; lamivudine, adefovir dipivoxil, tenofovir disproxil, tenofovir alafenamide, entecavir and telbivudine; has been approved for the treatment of chronic HBV infection in Malaysia. Since the sensitivity of the wild type HBV to nucleoside/nucleotide analogues approved or in development, is readily available the from cell culture model, tenofovir disoproxil was selected as the agent of choice in this study on chronic HBV patients with primary treatment failure [16-18]. This is because we postulated that in

patients with primary failure to entecavir, tenofovir disoproxil with its more potent anti-HBV activity when compared with the other approved oral treatment for chronic HBV should be effective even in those with primary treatment failure to entecavir. Furthermore, tenofovir disoproxil unlike lamivudine, entecavir and telbivudine that are nucleoside analogues, is a nucleotide analogue. Thus, theoretically tenofovir disoproxil should be effective in those with treatment failure to nucleoside analogues.

Here, although including only a small number of patients, we have provided clear evidence that tenofovir disoproxil is a safe and effective drug even for the treatment of chronic HBV patients with primary treatment failure to entecavir. Even in this select group of patients, tenofovir disoproxil is able to induce a response in all patients (100%) with primary treatment failure. Furthermore, normalization of serum ALT levels occurred in 85.7%. More importantly, 71.4% had combined normalization of serum ALT levels and undetectable serum HBV DNA level.

As this study only involved a small number of patients, more work will need to be performed before we can recommend the use of tenofovir on all patients with primary treatment failure. But, since the rate of primary treatment failure is relatively low, this is a difficult topic to study because enrolling a large group of patients will be necessary.

Another question that needs to be addressed with the use of tenofovir disoproxil in those with primary treatment failure is whether tenofovir disoproxil should be used as a sequential treatment or an add-on treatment for this select group of patients. This is because it has been demonstrated that adding adefovir dipivoxil to lamivudine in lamivudine-resistant mutations is much more effective in suppressing serum HBV DNA than switching over directly to adefovir dipivoxil monotherapy [19].

In conclusion, tenofovir disoproxil is a safe and effective choice for the treatment of chronic HBV patients with primary treatment failure to entecavir treatment.

References

1. Terrault NA, Lok ASF, McMahon BJ, et. al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018; 67: 1560-1599.
2. Chen CJ, Yang HI, Su J, et. al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA. 2006; 295: 65-73.
3. Iloeje UH, Yang HI, Du J, et al. Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. Gastroenterology. 2006; 130: 678-686.
4. Tang LSY, Covert E, Wilson E, et al. Chronic Hepatitis B Infection: A Review. JAMA. 2018; 319: 1802-1813.
5. Furquimd' Almeida A, Ho E, Van Hees S, et al. Clinical management of chronic hepatitis B: A concise overview. United European Gastroenterol J. 2022; 10: 115-123.
6. Liu LZ, Sun J, Hou J, et al. Improvements in the management of chronic hepatitis B virus infection. Expert Rev Gastroenterol Hepatol. 2018; 12: 1153-1166.
7. Yang YJ, Shim JH, Kim KM, et al. Assessment of current criteria for primary nonresponse in chronic hepatitis B patients receiving entecavir therapy. Hepatology. 2013; 59: 1303-1310.
8. Lok AS, MacMahon BJ. Chronic hepatitis B: update 2009. Hepatology. 2009; 50: 661-662.
9. EASL Clinical Practice Guidelines: Management of chronic hepatitis B. J Hepatol. 2009; 50: 227-242.
10. Mese S, Arikan M, Cakiris A, et. al. Role of the line probe assay INNO-LiPA HBV DR and ultradeep pyrosequencing in detecting resistance mutations to nucleoside/nucleotide analogues in viral samples isolated from chronic hepatitis B patients. J Gen Virol. 2013; 94: 2729-2738.
11. Chantratita W, Song KS, Pongthanapisith V, et. al. HBV/4DR 9G test and its comparison with INNO-LiPA HBV multi-DR test for detection of drug-resistant Hepatitis B virus. J Virol Methods. 2016; 237: 58-63.
12. Osiowy C, Villeneuve JP, Heathcote EJ, et al. Detection of rtN236T and rtA181V/T mutations associated with resistance to adefovir dipivoxil in samples from patients with chronic hepatitis B virus infection by the INNO-LiPA HBV DR line probe assay (version 2). J Clin Microbiol. 2006; 44: 1994-1997.
13. Lok AS, Zouzim F, Locarnini S, et. al. Monitoring drug resistance in chronic Hepatitis B virus (HBV)-infected patients during lamivudine therapy: evaluation of performance of INNO-LiPA HBV DR assay. J Clin Microbiol. 2002; 40: 3729-3734.
14. Leemans WF, Ter Borg MJ, De Man RA. Review article: success and failure of nuleoside and nucleotide analogues in chronic hepatitis B. Aliment Pharmacol Ther. 2007. 26: 171-182.
15. Schildgen O, Sirma H, Funk A, et. al. Variant of hepatitis B virus with primary resistance to adefovr. N Eng J Med. 2006; 354: 1807-1812.
16. Raney AK, Hamatake RK, Hong Z. Agents in clinical development for the treatment of chronic hepatitis B. Expert Opin Investig Drugs. 2003; 12: 1281-1295.
17. Farrell GC. Clinical potential of emerging new agents in hepatitis B. Drugs 2000; 60: 701-710.
18. Brunelle MN, Jacquard AC, Pichoud C, et al. Susceptibility to antivirals of a human HBV strain with mutations conferring resistance to both lamivudine and adefovir. Hepatology. 2005; 41: 1391-1398.
19. Gaia S, Barbon V, Smedile A, et. al. Lamivudine-resistant chronic hepatitis B: an observational study on adefovir in monotherapy or in combination with lamivudine. J Hepatol. 2008; 48: 540-547.