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EFFICACY OF TENOFOVIR AS FIRST-LINE ANTIVIRAL THERAPY IN CHRONIC HEPATITIS B INFECTION.

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ABSTRACT

To date, various antiviral therapy options are available in treatment of chronic hepatitis B (CHB). Choosing the right drug according to patients' profile is utmost crucial for optimal response, recovery and prevention of drug resistance. Tenofovir (TDF) is an approved first-line drug treatment for CHB. Several studies have reported on the safety and efficaciousness of TDF in treating CHB patients and achieving improvement. This narrative review article aimed to compile study evidences that highlighted the effectiveness of TDF as antiviral therapy in CHB patients. From the analysis done, it can be summarized that patients who have been undergoing TDF monotherapy or switched to TDF after other antiviral therapy had profound HBV DNA suppression level, no resistance detected and improved health condition. Based on this, TDF is strongly recommended to be continued as first-line treatment for CHB patients.

INTRODUCTION

Hepatitis B virus (HBV) infection is regarded as global health problem with approximately 370 million chronically infected worldwide [1]. The prevalence of chronic hepatitis B (CHB) infection has been correlated geographically by three categories; high endemicity (>8%), intermediate endemicity (2-8%), and low endemicity (<2%) [2]. High endemicity occurred in south-east Asia, China, sub-Saharan Africa, parts of the Middle East, the central Asian Republics, and some countries in Eastern Europe. It was estimated, 70 % to 90% of the population in these areas became HBV-infected before the age of 40 [3]. Most infections were reported to be transmitted perinatally from infected mothers [4].

Low endemicity areas include North America, Western and Northern Europe, Australia, and parts of South America. The remaining regions in the world such as Eastern and Southern Europe, Japan, and part of South America were considered as moderately endemic regions. In low endemicity areas, large number of HBV infections was acquired sexually, by injection of drug by multiple users or involving health care workers [5]. Mixed mode of transmission including infant, early childhood and adult transmission was observed mostly in the intermediate endemicity areas.

CHB infections lead to liver failure and cirrhosis in early stage and hepatocellular carcinoma (HCC) in advance stage. Despite the availability of treatment, prevention is always the superior way to control diseases. Passive immunoprophylaxis with hepatitis N immunoglobulin and hepatitis B vaccination at early infancy has effectively reduced the number of hepatitis B carriers in endemic areas [6]. In 1991, the World Health Organization (WHO) recommended that hepatitis B vaccination to be incorporated in national immunization system in all countries with a hepatitis B carrier prevalence of 8% or greater by 1995 and in all countries by 1997. The world's first universal HBV vaccination program kicked off in Taiwan in 1984 [7]. The end result of this vaccination program tremendously reduced hepatitis B carrier rate among children from 9.8% in 1984 to 1.3% in 1994.

Antiviral therapy using nucleos(t)ide analogues (NAs) is the current first-line treatment apart from interferon therapy which is more expensive and less effective for hepatitis B e antigen (HBeAg) negative patients. The ultimate goal of HBV antiviral therapy is to profoundly suppress viral replication, reduce the risk of drug resistance, prevent progression of disease, and thus improve survival [8,9]. Furthermore, maintaining undetectable level of HBV DNA and

HBeAg and hepatitis B surface antigen (HBsAg) seroconversion are also desired endpoint of antiviral therapy. The nucleoside analogues indicated for treatment of HBV infection are lamivudine (LAM), entecavir (ETV) and telbivudine (LdT) and nucleotide analogues are adefovir (ADV) and tenofovir disoproxil fumarate (TDF). However, emergence of drug-resistant mutants that are often associated with long term usage of lamivudine, adefovir and telbivudine has become a barrier to the success of treatment. Over the years, there has been accumulating evidences of successful HBV infection treatment by TDF and ETV. These two drugs are well recommended by the US Food and Drug Administration (FDA) as they have displayed an optimal resistance profile [9-10]. TDF in particular has not been reported to cause any

definitive resistance thus far. This review article aimed to summarize the efficacy of TDF as the first-line treatment choice with gathered evidences from literature and our own case study report.

ANTIVIRAL RESISTANCE IN CHB PATIENTS

Lamivudine (LAM)

LAM therapy has been associated with high rate of HBeAg seroconversion, normalization of alanine aminotransferase (ALT) levels and suppression of HBV viral load [11]. However, long-term usage of LAM in patients has increased the rate of HBV drug resistance with numerous evidences associated with this. Studies have consistently reported that minimum 20% of patients treated with LAM develop resistance to the drug by 1 year and 70% to 80% by 5 years after onset of treatment [12-14]. Commonly associated mutations due to administration of LAM are primary mutation M204 I/ M204V also known as YMDD mutation and secondary mutations L180M/ L180V, A181T and V173L. In addition, re-emergence of YMDD mutation has also been observed in patients who have been switched treatment from LAM to alternate nucleoside analog but re-introduced with LAM after a minimum of 3 months [15-16]. Thus, sequential LAM treatment in patients who have history of YMDD mutations should be avoided.

Telbivudine (LdT)

LdT was the fourth oral antiviral agent available for treatment of CHB when it obtained FDA approval in 2006 [17]. Incidence of LdT resistance in hepatitis B patients was documented as 5-6.8% within 1 year of treatment and 10-20% after 4 years of treatment [18-20]. Similar to LAM, treatment with LdT often caused emergence of YMDD mutation as signature mutation and L180M/ L180V mutations. When compared with LAM, many studies have provided evidences that LdT has superior antiviral and clinical efficacy [21-23].

Entecavir (ETV)

ETV is a first-line therapeutic drug used in treatment of CHB patients. It has a lower risk of developing resistance and induces greater suppression of HBV DNA within 24-36 weeks of therapy as compared to LAM and LdT [24]. After five years therapy, the rate of ETV resistance was reported to be approximately 1.25%. Nonetheless, while resistance in treatment-naïve patients is low, administration of ETV in pre-existing LAM-resistant patients develops ETV resistance at greater rate (57%) [25-26]. ETV shares two common mutations with LAM which are M240V /I and L180M/V apart from other reported mutations such as S202I, M250L/V T184G [27].

Adefovir (ADF)

ADF is referred as second line or add-on therapy to CHB patients in cases where LAM resistance has developed. Unlike ETV, ADF is safe to use in LAM-resistant patients as documented by a study where the probability of ADF resistance in 3 years treatment was reduced to as low as 0% by adding ADF to on-going LAM therapy as compared to ADF mono-therapy (16%) [28-30]. The known mutations associated with ADF monotherapy are N236T and A181T.

EFFICACY AND SAFETY OF TENOFOVIR (TDF)

Safety

TDF is a nucleotide analog that has been approved by the US FDA in 2008 for treatment of CHB. The recommended dosage is 300mg once a day. TDF acts by inhibiting the function of HBV DNA polymerase which is required by the virus to replicate. TDF is activated by diphosphorylation and competes with deoxynucleotide triphosphate (dNTP) to occupy the binding site of HBV polymerase enzyme, therefore terminating the chain elongation [31]. Minimal interference with human DNA polymerases is posed as TDF has higher affinity for viral DNA polymerase, thus it is safe to be administered in human [32]. Some recent research findings have concluded that TDF does not cause any severe adverse effect in humans, therefore safe to be used for long-term therapy [33-34]. Additionally, TDF has an outstanding resistance profile as no resistance has been reported to date even after 6 years of treatment and regardless of mono or combination therapy [35-37].

HBV DNA suppression

TDF has been proven to have an excellent performance in suppressing HBV DNA in CHB patients. In HBeAg-positive patients, those treated with TDF achieved viral suppression more rapidly than those treated with ETV with probability of complete suppression 18% vs. 11% at 6 months, 51% vs. 28% at 12 months and 72% vs. 39% at 18 months respectively [38]. Additionally, in LAM-resistant monoinfected HBV patients, TDF had significantly lowered HBV DNA level in CHB patients with 4–6 $\log^{10}$ reductions [39-41]. Multiple research findings of HBV DNA suppression in patients co-infected with HIV and HBV and treated with TDF were documented as well [42-43]. Suppression of HBV DNA to undetectable level was also observed in long-term treatment of TDF as evidenced by a study whereby over an eight year treatment with TDF, viral suppression was consistently maintained [44].

HBeAg seroconversion

HBeAg seroconversion is an important milestone in the management of HBeAg-positive CHB patients as it is associated with a reduced incidence of progressive liver inflammation, cirrhosis and HCC. At 1 year of treatment, patients who received TDF had a greater rate of HBeAg seroconversion (21%) as compared to ADF (18%) and by year two the HBeAg seroconversion by TDF increased by 26% [45].

CASE STUDY

In this review article we would like to include analysis findings of various drug treatments that were undertaken among 164 cases of HBV carriers in Malaysia to further support the efficacy of TDF on the patients. Previously, mutational study for drug resistance in P gene region and other mutations in S gene and C gene were conducted on the retrospective blood sera of these patients and results were published [27,46]. Complete information on the clinical symptom, HBV DNA level, treatment and current follow up status were able to be retrieved from 42 patients only. Among all the antiviral therapies, LAM had poor HBV DNA suppression rate (25%), presence of drug resistant mutation and low health recovery. There was no drug resistance documented for ETV treated patients, however the HBV suppression rate was lower (81.25%) compared to TDF (100%). HBeAg seroconversion incidence occurred in three TDF treated patients and one LAM treated patient. From the analysis, it was noticeable that all patients who have been undergoing treatment with TDF only or switched to TDF after LAM therapy had profound HBV DNA suppression, no resistance detected and improved health condition except one patient who died of HCC. However, the patient was non-compliant to the therapy and was reported to have stopped taking TDF after 1 month. The comparison of the effect of various drug

therapies on Malaysian Hepatitis B carriers from this study is summarized in Table 1.

DISCUSSION

The data (Table 1) provide evidence that support the significant efficacy of TDF in treating and managing CHB patients in both short-term and long-term therapy. Generally, rate of HBV DNA suppression within 1-4 years for TDF range from 68%-90%, ETV from 61%-92% and LAM and ADV from 12-21% [47-49]. Findings in Table 1 also indicated similar rate of HBV DNA suppression whereby TDF maintained its supremacy in reducing HBV DNA to undetectable level.

A high incidence of drug resistance mutations were observed in patients who were treated with LAM whereas TDF and ETV showed a high barrier to resistance. It was also observed that patients who initially had resistance to LAM, later showed good response and speed recovery with TDF similar to patients who received TDF monotherapy as indicated in patient status in Table 1. This proved the efficacy of TDF not only as a useful monotherapy but also for LAM -failure patients.

HBeAg seroconversion, being one of the ultimate goals in HBV treatment proven to frequently occur in TDF treated patients within one year of treatment.TDF is also well tolerated without serious adverse effect especially when administered in mono-infected patients. However there has been report of minor nephrotoxicity in HIV/HBV co-infected patients [50].On the other hand, TDF is classified as class B drug in regards to safety in pregnancy. A recent data revealed that exposure to TDF in pregnant women during the first trimester did not show any increase risk of birth defect to date. [51].

CONCLUSION

Based on literature review and our own findings, TDF has shown impeccable performance as first–line treatment for CHB patients. It is suggested that, patients who have not shown improvement in CHB treatment should be highly considered for TDF therapy. Efforts to continuously monitor the performance of TDF in future will be needed to observe any adverse effect or possible resistance to this drug.

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Table 1: Comparison of effect of various drug therapies on Malaysian Hepatitis B carriers

Antiviral Therapy	Number of patients	HBV DNA suppression (%)	Patient status	Drug resistance mutations	Number of HBeAg (+)	Number of HBeAg (-)	HBeAg seroconversion
LAM only	4	1 (25%)	-1 patient had condition worsen after LAM treatment and did not achieve HBV DNA suppression -1patient failed to achieve HBV DNA suppression even with 5 years of LAM therapy. -1 patient had declined HBV DNA level within 1 year of LAM treatment, however patient developed HCC and drug resistant mutation. Plan to switch to TDF. -1 patient who initially had undetectable HBV DNA after 1 year LAM treatment had reoccurrence of HBV DNA on subsequent years. Plan to switch to TDF	One patient had DR mutation: M2041/V detected in 2013 by PCR. Patient was prescribed LAM since 2008.	1	3	-1patient seroconverted after one year of LAM treatment
LAM to TDF	11	11 (100%)	All keeping well	Initial drug resistance due to LAM	4	7	-2 patients Seroconverted within 1 year of

				therapy such as L180M, M204V/I, V173L in 6 patients.			TDF therapy
TDF only	10	9 (90%)	All keeping well except 1 who was non-compliant to medicine died of HCC	None	4	6	-1patient seroconverted within 1 year of TDF mono-therapy
LAM to ADF	1	1 (100%)	Patient is keeping well	None	0	1	0
ETV only	17	14 (82.35%)	-1 patient died of HCC and was prescribed ETV for 1 month only (no HBV DNA suppression) -1 patient who initially achieved undetectable HBV DNA within 2 years ETV therapy had reactivation of HBV DNA in subsequent years. Suggested to switch to TDF -1 patient had persistent non-suppression of HBV DNA for almost 4 years of ETV therapy	None	7	10	0

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