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World J Gastroenterol 2007 August 14; 13(30): 4096-4099
World Journal of Gastroenterology ISSN 1007-7195

RAPID COMMUNICATION

Low-dose tenofovir is more potent than adefovir and is effective in controlling HBV viremia in chronic HBeAg-negative hepatitis B

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Received: 2007-04-23 Accepted: 2007-05-28

Abstract

AIM: To study the efficacy of tenofovir disoproxil fumarate (TDF) at low dose in a small open trial of chronic hepatitis B patients with advanced stage disease.

METHODS: Eleven patients were treated with TDF 75 mg for a median period of 80 (range, 24-576) wk and then 7 cases were shifted to an adefovir 10 mg treatment group. All patients had been pre-treated with lamivudine: 5 had YMDD resistant mutants and 6 wild-type virus. When TDF was started, 4 patients had low-level viremia and 6 were PCR-negative.

RESULTS: During TDF treatment, PCR remained negative in 10 patients, transaminase levels were normal and no significant viral breakthrough was observed. The drug was well tolerated in all cases. When TDF 75 mg was substituted with adefovir 10 mg, 3 out of 7 patients had a persistent viral rebound (2700-130 000 copies/mL), in whom lamivudine had to be reintroduced.

CONCLUSION: Low-dose TDF monotherapy can control HBV viremia for an extended period of time without the emergence of resistance and is more potent than adefovir at the standard dosage. The use of a reduced dose of TDF could diminish the cost of therapy in low-income countries, but further studies in a larger population and in HBeAg-positive subjects are needed.

Key words: Tenofovir; Chronic Hepatitis B; Adefovir; Nucleotide analogues; Low-income countries

Del Poggio P, Zaccanelli M, Oggionni M, Colombo S, Jamoletti C, Puhalo V. Low-dose tenofovir is more potent than adefovir and is effective in controlling HBV viremia in chronic HBeAg-negative hepatitis B. *World J Gastroenterol* 2007; 13(30): 4096-4099

http://www.wjgnet.com/1007-9327/13/4096.asp

INTRODUCTION

Tenofovir disoproxil fumarate (TDF) is a nucleotide analogue approved for the treatment of HIV infection and is structurally related to adefovir. TDF is also active against hepatitis B virus (HBV) and is equipotent to adefovir *in vitro*[1,2], but because of its lower nephrotoxicity, it can be used at higher dosage (e.g. 300 mg/d) and is more active than its parent compound against HBV *in vivo*[3-5]. TDF is equally effective against wild-type and lamivudine-resistant HBV[6] in HIV-coinfected patients[7], and may in the future replace adefovir in the therapy of hepatitis B. The main concern with TDF is the lack of safety data on the absence of nephrotoxicity of the 300 mg dose in long-term treatment. Although registration and large retrospective studies in HIV infection[8-10] have shown that the risk of deterioration of renal function is less than 3% , this problem could limit the use of TDF in decompensated cirrhotics with borderline renal function. The dose of 300 mg was chosen because these studies were conducted in coinfected patients with a dosage active against HIV, but there are no data on the susceptibility of HBV to lower TDF doses. Adefovir *per se* was initially used at 60-120 mg/d in order to achieve a significant HIV inhibition[11], a dosage well above the 10 mg dose approved in the treatment of hepatitis B. It is therefore feasible that TDF, like its parent drug adefovir, could be used at lower dosage. Another potential advantage of low-dose TDF would be the reduction of the cost of therapy in low-income countries, where the death toll of hepatitis B is worrisome. In consideration of this, we decided to test the efficacy of low-dose TDF in a small open trial of chronic HBeAg-negative hepatitis B patients with advanced stage disease.

MATERIALS AND METHODS

Eleven patients with chronic HBeAg-negative hepatitis B (7 males and 4 females; median age 63 years, range 40-77 years) were included in this study. The characteristics of the patients are described in Table 1. Nine had biopsy-

Table 1 Baseline characteristics of the patients

Patient	Sex	Age (yr)	Liver biopsy	Complica -tions	HBV DNA (pg/mL)[1]	LAM[3] (wk)	YMDD
1	F	77	Cirrhosis	HCC	8	96	M204I
2	M	40	CAH Ishak 9;2		2	156	M204V
3	M	63	Cirrhosis		Undetectable[2]	188	M204V
4	F	68	Cirrhosis	F2 esoph varices	1600	44	M204I
5	M	55	Cirrhosis		Undetectable[2]	104	M204V, L180M
6	F	58	Cirrhosis		450	88	WT
7	M	68	Cirrhosis	F2 esoph varices	64	76	WT
8	M	57	CAH Ishak 7; 4		162	116	WT
9	M	65	Cirrhosis		78	88	WT
10	M	58	Cirrhosis		0.2	52	WT
11	F	75	Cirrhosis		3.100	116	WT

[1]Basal HBV DNA (Digene Capture 2 Assay, sensitivity 0.2 pg/mL, equal to 105 copies/mL) before starting lamivudine; [2]Sample taken after ALT flare; [3]Duration of lamivudine treatment before starting tenofovir; esoph: esophageal.

proven well compensated cirrhosis with preserved hepatic function (Child-Pugh A) and two chronic active hepatitis with mild-moderate fibrosis, but with frequent ALT flares to more than 10 times normal value. Two patients had F2 oesophageal varices without previous episodes of bleeding and were on primary prophylaxis with Nadolol. One patient had a unifocal small hepatocellular carcinoma that was treated with percutaneous alcohol injection, resulting in a complete necrosis of the nodule. None of them had ascites, although one was on diuretic treatment with Canrenoate 100 mg daily orally. There were no comorbidities and the body mass index was under 30% in all cases. All 11 patients had been pre-treated with lamivudine 100 mg daily for a median duration of 96 (range 44-188) wk and 5 had developed mutations in the YMDD motif. Four had a single mutation (M204V in 2 cases and M204I in the other 2), one patient had a double mutation (M204V and L180M). The presence of YMDD resistance mutants was detected with the Innolipa assay (Innolipa Line Probe Assay, Innogenetics). At the time of emergence of resistance, 4 patients had normal levels of alanine aminotransferase (ALT) and negative serum branched HBV DNA (Versant HBV DNA 3.0 Bayer, sensitivity < 2000 copies/mL), although viral DNA could be detected by polymerase chain reaction (Innolipa Assay, Innogenetics with a sensitivity lower than 1000 copies/mL). One patient with a YMDD mutant had elevated ALT and serum HBV DNA of 4.8×10^6 copies/mL. The remaining 6 patients did not develop YMDD mutants and were PCR-negative with normal ALT during the entire treatment with lamivudine. They were shifted to TDF to prevent the emergence of YMDD resistant mutants, because at the time adefovir was not yet available to rescue the patients in case of development of lamivudine resistance. In all patients, lamivudine was withdrawn abruptly and substituted with TDF 75 mg daily orally, with no washout period. Tenofovir was given off label, with the consent of the patients, and was continued for a period of 80 (range 24-144) wk.

Table 2 Results of treatment with tenofovir disoproxil fumarate (TDF) in the individual patients

Patient (YMDD/ WT)	Basal HBV DNA[1] (cp/mL)	Duration of treatment with TDF (wk)	HBV DNA (end of TDF) (cp/mL)	Drug substituted for TDF	HBV DNA after substitution of TDF
1 (YMDD)	1000-2000	96	< 1000	ADV	130.000 cp/mL
2 (YMDD)	4.8×10^6	144	< 1000	ADV	No viral rebound
3 (YMDD)	1000-2000	56	< 1000	LAM	No viral rebound
4 (YMDD)	1000-2000	80	< 1000[2]	ADV + LAM	No viral rebound
5 (YMDD)	1000-2000	60	< 1000	ADV	No viral rebound
6 WT	< 1000	108	< 1000	ADV	No viral rebound
7 WT	< 1000	76	< 1000	ADV	21000 cp/mL
8 WT	< 1000	88	< 1000	ADV	2700 cp/mL
9 WT	< 1000	116	< 1000	ADV	No viral rebound
10 WT	< 1000	52	< 1000	LAM added to TDF	No viral rebound
11 WT	< 1000	24	< 1000	LAM	No viral rebound

[1]At the end of lamivudine treatment and before starting TDF; [2]After 8 mo of TDF, HBVDNA was unchanged but YMDD disappeared. Lamivudine was then added to TDF with prompt decrease of DNA below 1000 cp/mL.

When adefovir became available in the country, TDF was substituted with the former in 7 cases, with lamivudine alone or in combination with a nucleotide in the other 4 cases.

RESULTS

The results are shown in Table 2. Four of the 5 patients with YMDD mutants, including the patient with high viremia, became HBV DNA-negative by PCR assay after 8-24 wk of tenofovir treatment and remained negative throughout the entire period of treatment. One patient, who was HBV DNA-negative with the bDNA assay and PCR-positive at baseline, did not become PCR-negative during tenofovir treatment. After 32 wk of tenofovir monotherapy, she cleared the YMDD mutant and the wild-type virus reappeared, lamivudine was then reinstituted in addition to tenofovir, and subsequently she achieved PCR negativity. The six patients without lamivudine resistance were shifted to the tenofovir treatment group when their serum HBV DNA was undetectable by PCR and remained negative throughout the whole period of tenofovir treatment, with the exception of a transient viral blip in two cases at week 88 and 96 (5500 and 7500 copies/mL, respectively). Transaminase levels remained normal in all patients. The drug was well tolerated and no side effects were reported, in particular serum creatinine remained within normal limits in all cases. In 7 patients, tenofovir was substituted with adefovir 10 mg/d and a viral rebound was observed in 3 cases, one with previous lamivudine resistance and 2 with wild-type virus. The viral rebound was greater than 3 log in all the 3 cases and was controlled only after the addition of lamivudine to adefovir with

HBV DNA again undetectable by PCR. In an other 2 cases, lamivudine monotherapy was reinstituted after stopping tenofovir and no viral rebound was observed, but one patient died of hepatocellular carcinoma 96 wk after the reinstitution of lamivudine. One patient is still on tenofovir, but lamivudine was added after 52 wk to prevent the emergence of resistance to tenofovir and the patient is still PCR-negative at a follow-up of 100 wk.

DISCUSSION

In our small series of patients, a dose of TDF as low as 75 mg daily was able to suppress HBV viremia of both wild-type and lamivudine-resistant virus for a median period of 80 wk. All the patients were cirrhotic and/or with severe hepatitis and all achieved a good control of viremia, becoming PCR-negative with the Innolipa test, which has a sensitivity lower than 1000 copies/mL and in the range of 200-400 copies/mL. However, of the 5 patients with the YMDD resistant mutant, only one had a high level viremia before starting TDF, while the other 4 had low viremia (1000-2000 copies/mL). Also, the 6 patients with wild-type virus were shifted to TDF when their PCR was negative. Thus, the majority of patients had negative or low level viremia at the start of TDF, and this can be explained because they were all on lamivudine treatment at the time of the shift. No washout period was allowed for the fear of inducing a hepatitis flare in patients with severe disease and cirrhosis. Without an off-treatment baseline viremia, we could not demonstrate that low-dose TDF was able to control HBV replication from the beginning, but it is noteworthy that TDF maintained PCR negativity for an extended period of time in 10 of 11 (90.9%) patients. In these patients, we did not observe any persistent viral rebound, with the exception of two transient low-level viral blips that disappeared spontaneously without changing the TDF dose. This confirms the efficacy of low-dose TDF in controlling HBV viremia and also the high barrier to resistance of this drug, even at doses as low as 75 mg.

To date there have been only 2 reports of TDF-associated mutations conferring resistance to the drug[1,12]. This low level of resistance could be related to the fact that the great majority of the studies were on HIV-positive patients treated with other antiviral drugs, such as lamivudine and emtricitabine, in addition to TDF. Data on long-term TDF as monotherapy are scanty and this is probably the first report of an extended period of treatment with this drug at a dosage lower than 300 mg. It is also likely that a 75 mg dose of TDF is more potent than 10 mg of adefovir, and in fact 3 out of 7 patients had a persistent viral rebound when shifted from TDF to adefovir. This is in agreement with the findings of Van Bommel and Berg[13] who observed a reactivation of viral replication after replacement of TDF 300 mg with adefovir 10 mg. Despite being equipotent *in vitro*, adefovir is thus much less potent *in vivo* than TDF and can not retain the TDF response, whether it has been achieved with a 300 mg or with a 75 mg dose of TDF. This suggests that the greater potency of TDF is not only related to a higher dosage, but also to intrinsic differences in the antiviral effect of the two drugs, namely a different intracellular phosphorylation of TDF compared to adefovir[14,15], or a longer intracellular half-life of the phosphorylated form[16]. We can, therefore, conclude from our data that TDF at low dose can retain for a long period of time a full suppression of HBV viremia induced by the previous use of lamivudine.

This could have practical implications in two settings: the treatment of advanced stage hepatitis B in low-income countries and the treatment of cirrhotics with a borderline renal function. In the latter case, a low-dose nucleotide analogue could assure a good control of HBV viremia, while preserving renal function. The possibility of reducing the cost of therapy is also appealing for low-income countries, where the price of the other nucleos(t)ides, with the exception of lamivudine, would be prohibitive. Reducing the dose of TDF from 300 to 75 mg would bring the cost of one month of therapy down to US$100, which is 30% less than lamivudine and one fifth the cost of adefovir or entecavir. Even combining low-dose TDF and lamivudine, the monthly cost of therapy would be less than half the cost of adefovir or entecavir monotherapy.

Chronic hepatitis B virus affects more than 400 million people worldwide, the majority of which are living in low-income countries. Despite the fact that current HBV therapy is too expensive for these countries, no specific guidelines have been published for the developing world. Lamivudine is cheap and its cost will be further reduced when it will be available as a generic drug. Its use, however, is hampered by the emergence of resistance[4], and a report from Iran showed a good biochemical control in only half of the patients after one year of treatment[17]. Cost-effectiveness analysis of alfa-interferon has shown contradictory results for health care systems with tight budgetary constraints[18,19]. Lamivudine or adefovir monotherpay is not considered cost-effective[19], while data are lacking on entecavir and telbivudine. Moreover, alfa-interferon therapy has an additional cost of syringes and a need of refrigerating the drug which may limit its use in the developing world. Sequential treatment has been proposed as a cost-effective strategy, but there are disagreements on which drugs should be used in sequence. Kanwal *et al*[19] proposed lamivudine as the first drug with adefovir rescue for resistant cases, while Shepherd *et al*[20] opted for alfa-interferon followed by lamivudine. There is thus no consensus about the most cost-effective and affordable therapeutic strategy for hepatitis B in the developing world and the use of a potent drug like TDF at a reasonable cost would be greatly helpful.

Our findings show that low-dose TDF can control HBV viremia, but there are several limitations in this study and further evaluation of low-dose TDF in a larger population is needed. First, all the patients were HBeAg-negative and our results can not be generalized to HBeAg-positive patients, which are usually highly viremic. It is worth considering, however, that HbeAg-negative disease is on the rise in the developing world, especially in Asian countries[21], and that a higher viremia could be controlled by an initial period of full-dose TDF. Another limitation of our study is that analysis of viral dynamics during

TDF treatment has shown an important variability in viral decline among the treated patients, even when using a 300 mg dose[22]. It seems therefore likely that the use of a low-dose in a larger sample may encounter a greater variability of response than that found in our small series. An additional problem is a practical one: TDF tablets are very difficult to divide into four parts and may require a crushing apparatus or good sight and technical skill by the patient. Last but not least it should be considered that in the developing world, HBV is often associated to HIV and that a low-dose TDF could more easily induce resistance to this drug and compromise first line therapy of HIV[23]. It would therefore be advisable to use low-dose TDF only in advanced stage HBV disease when the prognosis of the underlying liver disease prevails over HIV infection, or alternatively to use TDF in association to low-cost antiretroviral therapy according to the World Health Organization Guidelines[24].

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