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BRIEF REPORT

Efficacy of telbivudine with conditional tenofovir intensification in patients with chronic hepatitis B: results from the 2-year roadmap strategy

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Abstract

Background: A 2-year roadmap study was conducted to evaluate the efficacy and safety of tenofovir intensification at Week 24 in patients with chronic hepatitis B (CHB) receiving telbivudine.

Scope: A prospective multicenter study was conducted in treatment-naive patients with hepatitis B e antigen (HBeAg)-positive CHB. All patients received telbivudine (600 mg/day) until Week 24. Thereafter, patients with detectable hepatitis B virus (HBV) DNA (≥300 copies/mL) were administered tenofovir (300 mg/day) plus telbivudine, and patients with undetectable HBV DNA continued telbivudine monotherapy until Week 104. The primary endpoint was the proportion of patients with undetectable HBV DNA (<300 copies/mL) at Weeks 52 and 104.

Findings: A total of 105 patients were enrolled in the trial, of which 100 were eligible for efficacy analysis. Undetectable HBV DNA levels were observed at Week 24 in 55 patients who continued on with telbivudine monotherapy. The remaining 45 patients with detectable HBV DNA received tenofovir add-on therapy. With monotherapy, 100% (55/55) and 94.5% (52/55) of patients achieved HBV DNA <300 copies/mL at Weeks 52 and 104, respectively; the corresponding values for patients with add-on therapy were 84.4% (38/45) and 93.3% (42/45). Overall, undetectable HBV DNA (<300 copies/mL) was found in 93% (93/100) and 94% (94/100) of patients at Weeks 52 and 104, respectively. HBeAg seroconversion rate was 44.4% (44/99) at Week 104 for the overall patient population. One patient in the monotherapy group and six in the intensification group demonstrated HBsAg clearance at Week 104. HBsAg seroconversion was observed in four patients at Week 104, all belonged to the tenofovir intensification group. Eight patients sustained HBsAg loss during a posttreatment follow-up period of 16 weeks. Alanine aminotransferase (ALT) normalization was constant in the telbivudine monotherapy group, whereas a progressive improvement was observed in the tenofovir intensification group. Two patients in the monotherapy and none in the intensification group experienced viral breakthrough by Week 104. There were no reports of myopathy in either group. The mean changes in estimated glomerular filtration rate (eGFR), estimated using the Modification of Diet in Renal Disease (MDRD) formula, from baseline to Week 104 were +6.145 mL/min/1.73 m^2 (p=0.0230) and +7.954 mL/min/1.73 m^2 (p=0.0154) in the telbivudine monotherapy and tenofovir intensification groups, respectively. The incidence of serious AEs was four in the telbivudine monotherapy and two in the tenofovir intensification group. The main limitation of this study was limited sample size, which made the power of the observation low, and the absence of a comparative subgroup to assess the progression of patients with detectable HBV DNA without treatment intensification.

Conclusions: Data from this 2-year roadmap study confirmed that telbivudine with add-on tenofovir was effective and well tolerated in patients with CHB. Telbivudine was associated with an improvement in eGFR from baseline in both the groups.

Keywords: chronic hepatitis B, glomerular filtration rate, hepatitis B e antigen, intensification, roadmap, telbivudine, tenofovir, virologic breakthrough

Abbreviations: ALT, alanine aminotransferase; CHB, chronic hepatitis B; CI, confidence interval; eGFR, estimated glomerular filtration rate; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; IIT, intention to treat; LOCF, last observation carried forward; MDRD, Modification of Diet in Renal Disease; mITT, modified intention to treat; NA, nucleoside analogue; OD, once daily; SD, standard deviation.

Citation

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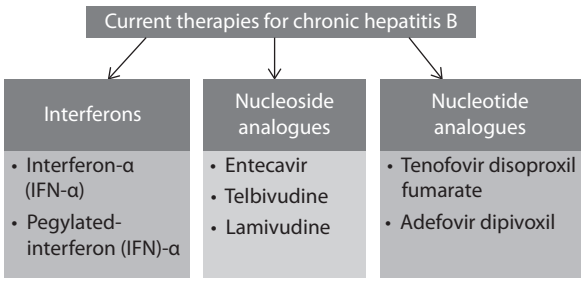
Introduction

Chronic hepatitis B (CHB) is a major area of concern worldwide, with approximately 240 million people being chronically infected with hepatitis B virus (HBV) and more than 780,000 deaths every year due to the acute or chronic consequences of hepatitis B [1]. Over one million patients suffering from CHB die every year with end-stage liver disease, including cirrhosis and hepatocellular carcinoma [2,3]. The emergence of resistance due to prolonged nucleoside analogues (NAs) therapy or incomplete suppression of HBV still remains an important challenge [4].

Over the past few decades, the treatment landscape for CHB has changed from monotherapy to the conditional addition of other antiviral drugs, by on-treatment monitoring of serum HBV DNA and/or HBsAg levels. This concept, widely known as "roadmap strategy," may improve efficacy and prevent the emergence of resistance [2,5–7]. In addition, sustained hepatitis B e antigen (HBeAg) seroconversion in these patients may improve long-term outcomes through the decreased risk of hepatic complications compared with those without a sustained seroconversion [8]. Currently, several antiviral drugs are available for the treatment of CHB, which include interferons, telbivudine, lamivudine, tenofovir, entecavir, and adefovir [9–11] (Figure 1). Telbivudine is a β-L-nucleoside analog indicated for the treatment of CHB with evident viral replication and elevated alanine aminotransferase (ALT) levels. The superiority of telbivudine over lamivudine has been proven in the GLOBE trial [12,13]. A recent network meta-analysis reported that telbivudine had a superior efficacy as compared with adefovir, entecavir, and lamivudine in HBeAg seroconversion [14]. Tenofovir disoproxil fumarate is an acyclic NA of adenosine monophosphate [15] with potent antiviral activity against HBV and is recommended as an add on in case of telbivudine resistance [2]. As per APASL 2015 guidelines, patients with CHB receiving adefovir or lamivudine or telbivudine treatment would require an early detection and modification of therapy to optimize long-term outcomes [16]. The present study was performed to determine the safety and efficacy of telbivudine with or without treatment intensification by tenofovir addition at Week 24 in patients with HBeAg positive CHB. This was the first prospective study to monitor the treatment response and conditional intensification with tenofovir. The 1-year results have been published earlier [17]; in this paper, we present the 2-year results of the telbivudine roadmap study.

Figure 1. Current approved therapies for chronic hepatitis B [9–11].



Materials and Methods

Study design

This was a prospective, 2-year, multinational, single-arm, and open-label phase IV long-term study [17] that enrolled a total of 105 patients between April 2008 and September 2011. Patients were enrolled from 17 centers in five countries: Argentina (3), Brazil (4), Germany (4), Hong Kong (2), and Thailand (4). Blood samples were collected from patients during "screening visit," "baseline visit," "treatment visits," and "posttreatment visits." At screening visit, 40 mL of blood was collected from each patient to test if hepatitis C virus, hepatitis D virus, and HIV are present in the blood sample. Patients were not enrolled in the study if any of these viruses were detected in the blood samples. Blood tests were done to detect "e" antigen of the virus. At baseline visit, 35 mL of blood was collected per patient for laboratory testing of HBV. During treatment visits at Weeks 2, 4, 8, 12, 16, 24, 26, 30, 40, 48, 52, 60, 68, 76, 86, 96, and 104, blood samples (20–40 mL) were collected, frozen, and stored. The stored blood samples were used for the detection and sequencing of HBV. During posttreatment follow-up visits at Weeks 108, 112, 116, and 120, blood samples (25 mL) were collected for laboratory testing. All patients received telbivudine (600 mg/day) until Week 24, and if the HBV DNA levels were ≥300 copies/mL, tenofovir (300 mg/day) was added at Week 26. The posttreatment follow-up was planned for 16 weeks after Week 104. Informed consent was obtained from each patient

included in this study and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

Patients

The study enrolled patients with CHB of either sex, aged ≥18 years and who had detectable HBsAg at the screening visit and for at least 6 months prior to inclusion, were HBeAg-positive and HBeAb-negative, and had serum HBV DNA ≥5 $\log_{10}$ copies/mL, elevated serum ALT (1.3–10 × upper normal limit), and evidence of chronic liver inflammation. Patients were excluded if they had a coinfection with hepatitis C virus, hepatitis D virus, HIV, or other causes of chronic liver disease (other than CHB) [17].

Efficacy assessment

The primary endpoint was to determine the proportion of patients with undetectable HBV DNA (<300 copies/mL) at Weeks 52 and 104. The secondary endpoints included the rate of virologic breakthrough, defined as HBV DNA ≥1 $\log_{10}$ copies/mL from nadir on two consecutive visits, up to Week 104; the rate of treatment-emergent HBV resistance confirmed by genotyping, with viral breakthrough (defined as HBV DNA ≥1 $\log_{10}$ copies/mL from nadir on two consecutive visits) up to Week 104; reduction in HBV DNA (<300 copies/mL) from baseline over the course of the study; ALT normalization at Weeks 24, 52, and 104; and HBeAg and HBsAg loss and seroconversion at Weeks 52 and 104.

Safety assessment

The safety analysis included the monitoring of adverse events (AEs) based on clinical and laboratory evaluations and their correlation with the study medication based on the investigator's assessment. The safety population included all patients who received at least one dose of the study medication (intention to treat [ITT] population) and had at least one post-baseline safety assessment. GFR was estimated using both the Cockcroft-Gault and Modification of Diet in Renal Disease (MDRD) formulae at Weeks 52 and 104.

Statistical analyses

A two-sided paired *t*-test was used to assess the change in GFR from baseline. All statistical analyses were performed using SAS® version 9.3 (SAS Institute, Inc., Cary, NC, USA).

Results

Patient disposition and baseline characteristics

A total of 105 patients were enrolled in the trial, of which 100 were eligible for the efficacy analysis (Figure 2). The patient demographics and baseline characteristics have been previously reported [17]. Eighty-eight patients completed the treatment phase at Week 104. In total 103, 101, and 85 patients completed treatment at Week 26, Week 52, and posttreatment follow-up period of 16 weeks, respectively.

Efficacy

At Week 24, 55 of 100 (55%) patients had undetectable HBV DNA (<300 copies/mL) and continued to receive telbivudine. Of these, all 55 patients had HBV DNA <300 copies/mL at Week 52, and 52 (94.5%) patients still had HBV DNA <300 copies/mL at Week 104. The remaining 45 patients with HBV DNA ≥300 copies/mL at Week 24 received tenofovir 300 mg along with telbivudine 600 mg after Week 26 until the end of the study (104 weeks). Of these 45 patients, serum HBV DNA was undetectable (HBV DNA <300 copies/mL) in 38 (84%) and 42 (93%) patients at Week 52 and Week 104, respectively.

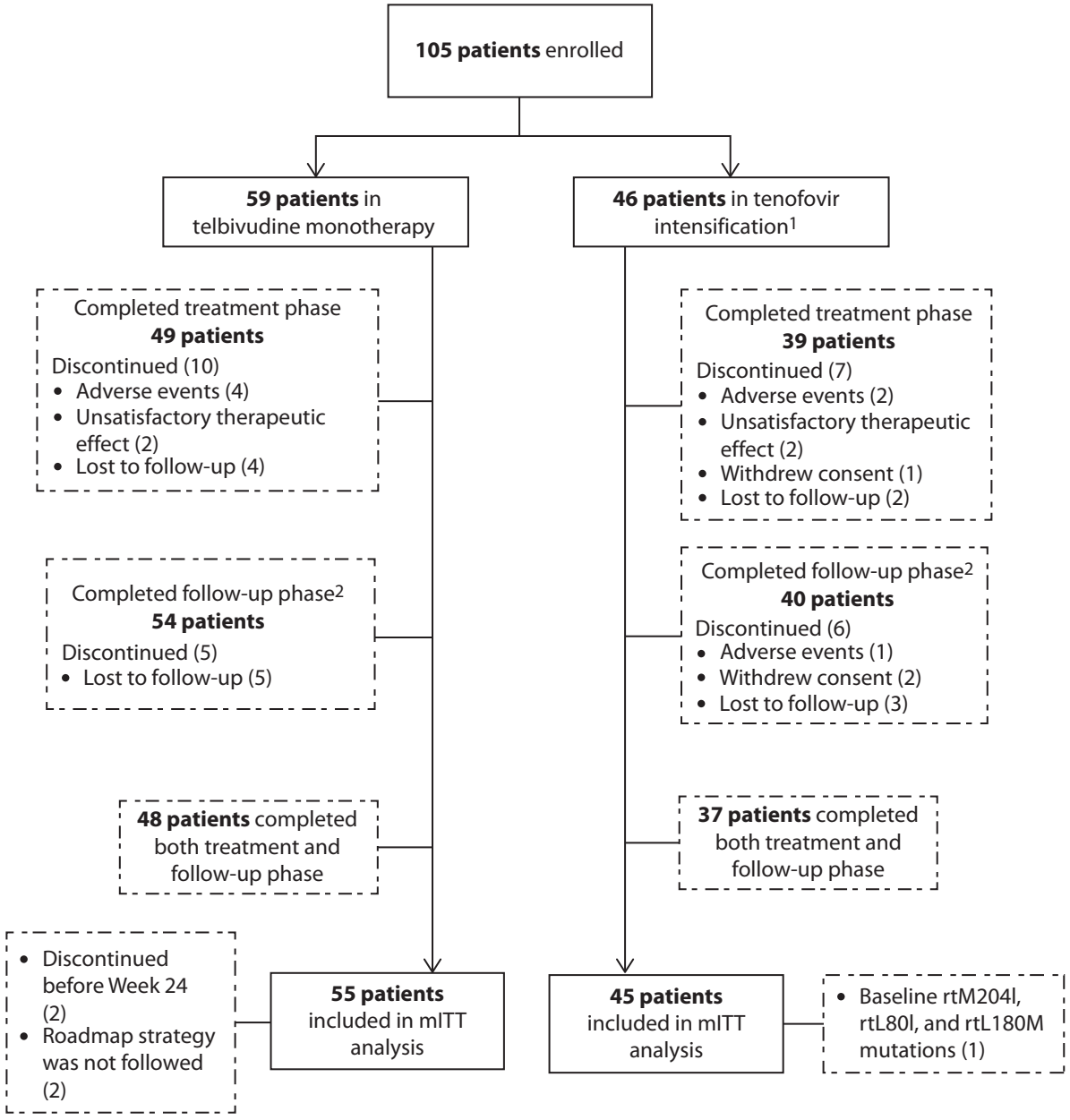
Overall in all patients enrolled, the primary endpoint of undetectable HBV DNA (<300 copies/mL) was found to be 93% (93/100) at Week 52 and 94% (94/100) at Week 104. Table 1 summarizes the primary and secondary endpoints at Weeks 52 and 104. The reduction in serum HBV DNA was statistically significant from baseline up to Week 104 (p<0.0001; Figure 3). At Week 52, the mean reduction, by last observation carried forward, in HBV DNA was 6.2 and 7.4 $\log_{10}$ copies/mL whereas at Week 104, the reduction compared with baseline was 6.1 and 7.5 $\log_{10}$ copies/mL in the telbivudine monotherapy and tenofovir intensification groups, respectively.

The rate of HBeAg loss at Week 104 was slightly improved from that at Week 52 in both the telbivudine monotherapy (70.9% from 65.5%) and tenofovir intensification (25.0% from 15.9%) groups. A similar pattern of improvement was also observed with HBeAg seroconversion at these time points.

HBsAg loss was observed in six patients at Week 52 and in seven patients (six from tenofovir intensification and one from telbivudine monotherapy group) by Week 104. Similarly, HBsAg seroconversion was observed in three patients at Week 52 and four patients at Week 104, all belonging to the tenofovir intensification group. In total, eight patients sustained HBsAg loss during the follow-up period (one patient at Week 116 and seven patients at Week 120).

At Week 104, four of the seven patients with HBsAg loss and two of the four patients with HBsAg seroconversion presented with HBV DNA <300 copies, HBeAg seroconversion, and ALT normalization. Overall, the rate of ALT normalization consistently improved from 66% at Week 24 to 77% at Week 52 and 84% at Week 104. ALT normalization was constant in the telbivudine group (86%, 87%, and 87%, respectively at Weeks 24, 52, and 104), whereas a progressive improvement in ALT normalization was observed in the tenofovir intensification group (42%, 64%, and 80%, respectively at Weeks 24, 52, and 104).

Figure 2. Patient disposition.



[1]Patients in the tenofovir intensification group also received telbivudine until Week 24.
[2]Investigators provided follow-up medical care according to the local standard of care for patients who were prematurely withdrawn from the study.
mITT, modified intention to treat. Efficacy analysis was performed on the mITT population, which excluded patients who discontinued before Week 24 or did not take tenofovir despite detectable HBV DNA. The mITT population also excluded patients who showed a baseline HBV DNA mutation.

Viral breakthrough

Until Week 52, none of the patients in this study experienced viral breakthrough and genotypic resistance [17]. However, by Week 104, two patients with baseline HBV DNA > 9 $\log_{10}$ copies/mL in the telbivudine monotherapy group had viral breakthrough and treatment-emergent genotypic resistance. None of the patients in the tenofovir intensification group experienced viral breakthrough or resistance throughout the study period (104 weeks).

Safety

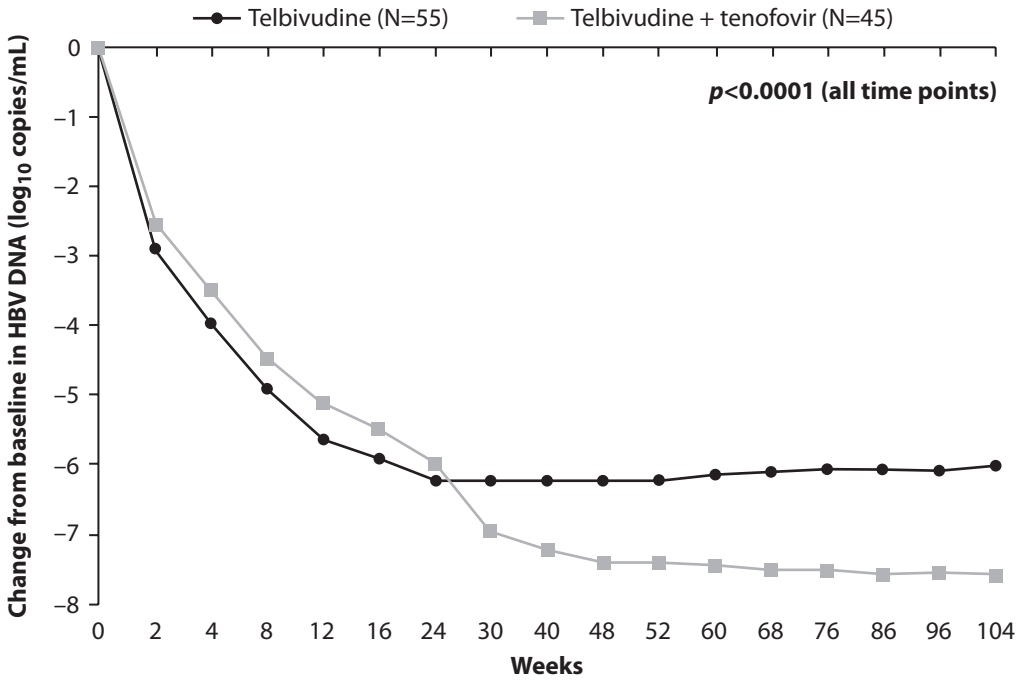
The incidence of AEs is summarized in Table 2. The majority (58.1%) of AEs were mild, while 13.3% were moderate and only 4.8% were severe in intensity. A total of 28 (27%) patients

Table 1. Comparison of various efficacy endpoints in mITT population.

Efficacy endpoint, n (%)		Telbivudine monotherapy N=55	95% CI	Telbivudine + Tenofovir N=45	95% CI	Overall N=100	95% CI
HBV DNA <300 copies/mL	Week 2	1/55 (1.8)	(0, 5.4)	—	NA	1/100 (1.0)	(0, 3)
	Week 24	55/55 (100)	(100, 100)	—	NA	55/100 (55.0)	(45.3, 64.8)
	Week 104	52/55 (94.5)	(88.5, 100)	42/45 (93.3)	(86.1, 100)	94/100 (94.0)	(89.4, 98.7)
HBeAg loss	Week 104	39/55 (70.9)	(58.9, 82.9)	11/44 (25.0)	(12.2, 37.8)	50/99 (50.5)	(40.7, 60.4)
HBeAg seroconversion	Week 104	37/55 (67.3)	(54.9, 79.7)	7/44 (15.9)	(5.1, 26.7)	44/99 (44.4)	(34.7, 54.2)
HBsAg loss	Week 104	1/55 (1.8)	(0.0, 5.4)	6/44 (13.6)	(3.5, 23.8)	7/99 (7.1)	(2, 12.1)
HBsAg seroconversion	Week 104	0/55 (0.0)	NA	4/44 (9.1)	(0.6, 17.6)	4/99 (4.0)	(0.2, 7.9)
Virologic breakthrough	Week 104	2/55 (3.6)	(0, 8.6)	0/45 (0.0)	NA	2/100 (2.0)	(0, 4.7)
ALT normalization	Week 104	48/55 (87.3)	(78.5, 96.1)	36/45 (80.0)	(68.3, 91.7)	84/100 (84.0)	(76.8, 91.2)

CI, confidence interval; mITT, modified intention to treat. The primary endpoint was to determine the proportion of patients with undetectable HBV DNA (<300 copies/mL) by COBAS Amplicor HBV monitor assay (Roche Molecular Systems, Branchburg, NJ, USA) at Weeks 52 and 104.

Figure 3. Change in HBV DNA levels from baseline to Week 104 (mITT population).



All patients received telbivudine monotherapy until Week 24

HBV, hepatitis B virus; mITT, modified intention to treat.

reported AEs that were related to the study medication. No deaths were reported in any of the study groups. Overall, the incidence of serious AEs was low (5.7%, 6/105): four in the telbivudine monotherapy group and two in the tenofovir intensification group. None of the serious AEs were considered to be related to the study medication.

In total, 17 patients experienced myalgia, the majority (n=13) being in the telbivudine monotherapy group and 4 in the tenofovir intensification group. Out of 17, myalgia events resolved in 13 patients while continuing treatment; events remained ongoing for two patients, and two patients discontinued treatment. Four patients reported muscle

Table 2. Most common adverse events at Week 104.

n (%)	Telbivudine monotherapy N=59	Telbivudine + Tenofovir N=46			Overall N=105
		Telbivudine monotherapy period	Telbivudine + Tenofovir period	Total	
Total no. (%) of patients with SAE	3 (5.1)	1 (2.2)	2 (4.3)	3 (6.5)	6 (5.7)
Total no. (%) of patients with any AE	50 (84.7)	23 (50.0)	25 (54.3)	31 (67.4)	81 (77.1)
Myalgia	13 (22.0)	3 (6.5)	3 (6.5)	4 (8.7)	17 (16.2)
Upper respiratory tract infection	8 (13.6)	4 (8.7)	2 (4.3)	6 (13.0)	14 (13.3)
Headache	7 (11.9)	5 (10.9)	3 (6.5)	6 (13.0)	13 (12.4)
Dyspepsia	6 (10.2)	0	4 (8.7)	4 (8.7)	10 (9.5)
Arthralgia	2 (3.4)	2 (4.3)	6 (13.0)	7 (15.2)	9 (8.6)
Cough	2 (3.4)	2 (4.3)	3 (6.5)	5 (10.9)	7 (6.7)
Nasopharyngitis	6 (10.2)	0	1 (2.2)	1 (2.2)	7 (6.7)
Diarrhea	3 (5.1)	1 (2.2)	2 (4.3)	3 (6.5)	6 (5.7)
Pyrexia	5 (8.5)	1 (2.2)	0	1 (2.2)	6 (5.7)
Dizziness	4 (6.8)	1 (2.2)	0	1 (2.2)	5 (4.8)
Fatigue	4 (6.8)	1 (2.2)	0	1 (2.2)	5 (4.8)
Nausea	2 (3.4)	0	3 (6.5)	3 (6.5)	5 (4.8)
Upper abdominal pain	0	3 (6.5)	1 (2.2)	4 (8.7)	4 (3.8)
Decreased appetite	1 (1.7)	0	3 (6.5)	3 (6.5)	4 (3.8)
Muscular weakness	1 (1.7)	0	3 (6.5)	3 (6.5)	4 (3.8)
Pain in extremity	3 (5.1)	1 (2.2)	0	1 (2.2)	4 (3.8)
Vomiting	1 (1.7)	0	3 (6.5)	3 (6.5)	4 (3.8)
Influenza	3 (5.1)	0	0	0	3 (2.9)

AE, adverse event; SAE, serious adverse event.

Units of measurement

Measurement	Units
Undetectable HBV DNA	copies/mL
Dose (telbivudine or tenofovir)	mg/day
Estimated glomerular filtration rate	mL/min/1.73 m^2
Alanine aminotransferase level	U/L
Blood creatinine level	μmol/L
Virologic breakthrough	log_{10} copies/mL

weakness, one in the telbivudine monotherapy group and three in the tenofovir intensification group. Five patients from the telbivudine monotherapy group and two patients from the tenofovir intensification group had grade 3 or 4 creatine kinase levels. One patient from the tenofovir intensification group reported elevated blood creatinine levels (232 μmol/L) at Week 97, which returned to 91 μmol/L within 5 days. On-treatment ALT flare, defined as ALT elevation >2 × baseline and ALT elevation >10 × upper normal limit, was observed in two patients, both from the tenofovir intensification group, at Weeks 4 and 8 after initiation of the initial treatment, whereas six patients, three from each group, had ALT flares during the posttreatment follow-up phase. For the ITT population, the mean change in GFR at Week 104, calculated by the MDRD and Cockcroft-Gault formulae, in the telbivudine monotherapy group was +6.145 mL/min/1.73 m^2 (p=0.0230) and +6.268 mL/min/1.73 m^2 (p=0.0072), whereas the mean change in GFR in the tenofovir intensification group was +7.954 mL/min/1.73 m^2 (p=0.0154) and +4.372 mL/min/1.73 m^2 (p=0.1415), respectively.

Discussion

The results from the present prospective randomized study support the concept of monitoring virologic response at Week 24 and conditional intensification of therapy, as recommended by current practice and international guideline [2]. Notably, 94.5% of patients, who had undetectable HBV DNA (<300 copies/mL) at Week 24 and continued to receive telbivudine, had undetectable HBV DNA at Week 104. HBV DNA levels were mostly consistent in the telbivudine monotherapy group throughout the study period, whereas the addition of tenofovir in the intensification group facilitated further reduction over Weeks 52 and 104.

Consistent with the GLOBE study, which compared the efficacy and safety of telbivudine versus lamivudine over 2 years in patients with CHB, our prospective results demonstrated that undetectable HBV DNA at Week 24 is a strong on-treatment predictor of treatment response by Week 104 [13]. Patients with baseline HBV DNA <9 log_{10} copies/mL were most likely to respond to telbivudine monotherapy at Week 24. Although the baseline HBV DNA is not considered for treatment decision as

per the roadmap algorithm, this observation could be of value in predicting treatment intensification [6].

Overall, the secondary efficacy endpoint of HBeAg and HBsAg clearance or seroconversion demonstrates improvement at Week 104 compared with Week 52. The ideal endpoint of HBsAg clearance was reached by 7% of patients. HBsAg clearance was greater in patients with tenofovir intensification than with telbivudine alone. Based on the levels of HBV DNA at Week 24, this is probably due to the addition of tenofovir, in patients receiving telbivudine. Telbivudine plus tenofovir showed better results than telbivudine monotherapy with regards to HBsAg loss, which might be due to a synergistic antiviral effect between telbivudine and tenofovir, and this warrants long-term investigation [17]. The rates of HBeAg clearance and seroconversion were comparatively higher in those patients with undetectable Week 24 viremia (HBV DNA <300 copies/mL) who remained on telbivudine monotherapy. Therefore, effective clearance and seroconversion of HBeAg appears to be a function of early and complete virologic suppression.

Overall, resistance rates in both the treatments were low. Only two patients from the telbivudine monotherapy group and none from the tenofovir intensification group had viral breakthrough and HBV resistance, supporting the roadmap strategy. These two patients had high baseline HBV DNA (>9 $\log_{10}$ copies/mL), and by considering the subset of patients with baseline HBV DNA <9 $\log_{10}$ copies/mL, none had viral breakthrough or resistance at Week 104. Baseline HBV DNA (<9 $\log_{10}$ copies/mL) could also be a predictor of low resistance, as previously demonstrated in the GLOBE study [13].

The European Association for the Study of the Liver (EASL 2012) guideline for CHB treatment recommends the addition of tenofovir in patients with telbivudine resistance, which also warrants long-term safety [2]. In this study, both telbivudine and tenofovir intensification were well tolerated for 104 weeks. There were no treatment-emergent events with the long-term treatment and no safety concerns with the tenofovir intensification. The commonly reported AE in the monotherapy was myalgia. There were no reports of myopathy.

HBV is associated with extrahepatic manifestations, most important being glomerulonephritis [18]. It is reported that 15%–30% of patients with CHB have either baseline renal dysfunction or comorbidities related to CKD (chronic kidney disease), such as diabetes and hypertension [19]. As per international guideline, patients starting therapy with NAs should be tested for serum creatinine levels and estimated creatinine clearance before treatment [2]. Appropriate dosing adjustment is recommended while using NAs in patients with creatinine clearance <50 mL/min as NAs are cleared by kidneys [2]. Except for telbivudine, which seems to improve creatinine clearance, minimal rates of renal function decline were associated with other NAs [2]. Monitoring of adverse renal effects is recommended while using tenofovir and adefovir in patients with CHB as they have high potential for nephrotoxicity [2]. In the present study, telbivudine therapy was associated with an improvement in eGFR from baseline to Week 104 in both telbivudine monotherapy and tenofovir add-on therapy. These findings are consistent with the 1-year results reported from this study [17]. The improvement in eGFR with telbivudine treatment was also reported in earlier studies [19,20]; however in contrast there was decline in eGFR and renal function observed with tenofovir in previously published studies and therefore regular monitoring of renal parameters is recommended with the use of tenofovir [21–23].

The main limitation of the study is limited sample size, which makes the power of the observation low, and the absence of a comparative subgroup to assess the progression of patients with detectable HBV DNA without treatment intensification. Quantitative analysis of HBsAg decline compared with baseline at Week 24 in two groups would be helpful to understand he observed high HBsAg loss rates. In this study, there was no control group of telbivudine monotherapy for patients who had detectable HBV DNA (≥300 copies/mL) at Week 24 and continued the monotherapy. Therefore, as per study design there was no comparator to evaluate the 2-year treatment effect of tenofovir intensification versus continued telbivudine monotherapy in patients with detectable HBV DNA at Week 24.

In conclusion, the 2-year results from the telbivudine roadmap study confirm the importance of on-treatment monitoring and that the addition of tenofovir to telbivudine in CHB patients with a partial or inadequate early virologic response may improve long-term outcomes. The conditional addition of tenofovir results in high rates of HBV DNA suppression and HBeAg seroconversion. None of the patients in the tenofovir intensification group experienced virologic breakthrough or viral resistance throughout the 104 weeks of treatment. The overall safety profile during the study was favorable, suggesting that this conditional add-on treatment based on the "roadmap concept" may represent an optimal therapeutic approach in HBeAg-positive patients with CHB.

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