Liver INTERNATIONAL
OFFICIAL JOURNAL OF THE INTERNATIONAL ASSOCIATION FOR THE STUDY OF THE LIVER

Liver International ISSN 1478-3223

CLINICAL STUDIES

Efficacy of switching to telbivudine in chronic hepatitis B patients treated previously with lamivudine

Rifaat Safadi[1,2], Qing Xie[3], Yagang Chen[4], You-Kuan Yin[5], Lai Wei[6], Seong Gyu Hwang[7], Eli Zuckerman[8], Ji-Dong Jia[9] and Patricia Lopez[10]

1 Hadassah Medical Center, Jerusalem, Israel
2 Holy Family Hospital, Nazareth, Israel
3 Department of Infectious Diseases, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China
4 The First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, China
5 Huashan Hospital, Shanghai, China
6 People's Hospital, Peking University, Beijing, China
7 CHA Bundang Medical Center, CHA University, Gyeonggi-Do, Korea
8 Liver Unit in Carmel Medical Center, Haifa, Israel
9 Beijing Friendship Hospital, Capital Medical University, Beijing, China
10 Novartis Pharma AG, Basel, Switzerland

Keywords
chronic hepatitis B – HBV DNA – lamivudine – nucleoside analogue – telbivudine switch

Correspondence
Rifaat Safadi, Holy Family Hospital, Nazareth, Israel
Tel: +972 4 6508900
Fax: +972 4 6508922
e-mail: safadi@hadassah.org.il

Received 28 May 2010
Accepted 23 September 2010

DOI:10.1111/j.1478-3231.2010.02360.x

Abstract

Background: Telbivudine showed greater antiviral suppression than lamivudine in phase II and III clinical trials. *Aims:* The present phase IIIb, randomized, double-blind, multicentre global trial assessed the antiviral efficacy and safety of telbivudine switch in chronic hepatitis B (CHB) patients who exhibited persistent viraemia under lamivudine therapy. *Methods:* HBeAg-positive and HBeAg-negative adult patients ($N = 246$) with persistent viraemia [hepatitis B virus (HBV) DNA>3 $\log_{10}$ copies/ml] under lamivudine treatment for 12–52 weeks were randomized (1:1) to continue lamivudine 100 mg/day or switch to telbivudine 600 mg/day for 1 year. Primary endpoint was the reduction in serum HBV DNA levels from baseline at Week 24. *Results:* The mean reduction in serum HBV DNA levels from baseline with telbivudine was significantly higher than lamivudine at Week 24 (-1.9 ± 0.18 vs. -0.9 ± 0.27 $\log_{10}$ copies/ml; $P<0.001$) and maintained through 1 year. The rate of treatment failure was significantly lower ($P<0.001$) for patients who switched to telbivudine (5%) compared with those who continued lamivudine (20%) after 52 weeks of treatment. In the telbivudine group, treatment failure occurred in only five patients with >24 weeks of prior lamivudine treatment, all associated with pre-existent lamivudine-resistant mutations. Genotypic resistance rates were higher in patients continuing lamivudine compared with those who switched to telbivudine with <24 weeks of lamivudine exposure. Both treatments were well tolerated with similar safety profiles. *Conclusions:* Early (≤24 weeks) switch to telbivudine improves virological outcomes in CHB patients with persistent viral replication under lamivudine treatment.

Chronic hepatitis B (CHB) is a significant health problem worldwide. It is estimated that 5% of the total world population is infected with hepatitis B virus (HBV), and among these, ∼500 000 die of HBV-related complications [cirrhosis and hepatocellular carcinoma (HCC)] (1). Recent studies established a possible link between the level of persistent viral replication and the development of CHB complications (2–4). Therefore, the main goal of CHB treatment is the achievement of early and durable viral suppression, as described in current international guidelines (5). Drugs available for the treatment of CHB include oral nucleoside analogues (lamivudine, entecavir and telbivudine), nucleotide analogues (adefovir dipivoxil and tenofovir) and an immunomodulatory agent (interferon/peginterferon-α) (6).

Lamivudine is the most commonly prescribed drug for CHB therapy, with treatment extended beyond 1 year in most patients. During the first year of lamivudine therapy, HBV strains resistant to lamivudine may develop in 15–30% patients, leading to treatment failure (7). The GLOBE trial compared the efficacy and safety of telbivudine vs. lamivudine treatment over 2 years in patients with

CHB and demonstrated a significantly higher efficacy for telbivudine and similar safety to lamivudine in HBeAg-positive and HBeAg-negative patients (8, 9).

The aim of the present study was to compare the antiviral efficacy and safety of telbivudine switch vs. continued lamivudine treatment in patients with persistent viraemia after 12–52 weeks of previous lamivudine treatment.

Patients and methods

Patients

Male and female adult CHB patients (aged 18–70 years) with HBeAg-positive or HBeAg-negative compensated liver disease participated in this phase IIIb, randomized, double-blind, multicentre global trial (40 centres). Key inclusion criteria were prior lamivudine treatment for 12–52 weeks, serum HBV DNA $>3\log_{10}$ copies/ml and serum alanine transferase (ALT) <10 times the upper limit of normal (ULN). Patients were excluded if they had: co-infection with hepatitis C, D or HIV; evidence of hepatic decompensation, pancreatitis or HCC; previous treatment for CHB with nucleos(t)ide analogues except lamivudine; treatment with interferon-α or other immunomodulators within the past 12 months; other forms of liver disease; serum creatinine level $\geq$1.5 mg/dl; prothrombin time >3 s; serum albumin level <3.3 g/dl; or total bilirubin level ≥ 2.0 mg/dl. Eligible patients with a serum α-feto protein >50 ng/ml required exclusion owing to the possibility of underlying HCC.

Study design

All eligible patients who were treated previously with lamivudine (12–52 weeks) were randomized (1:1, by an IVRS system) to either switch to once-daily administration of oral telbivudine 600 mg (tablet) or to continue lamivudine 100 mg for 52 weeks (Fig. 1a). Patients provided written informed consent. This study conformed with the ethics principles of the Declaration of Helsinki, Good Clinical Practice guidelines and applicable local regulatory requirements, including institutional-review board approval.

Efficacy and safety assessments

Primary efficacy endpoint was a reduction in serum HBV DNA levels from the study baseline at Week 24. Secondary efficacy endpoints evaluated at Weeks 24 and 52 were serum HBV DNA undetectable by polymerase chain reaction (PCR) (<300 copies/ml), ALT normalization, HBeAg loss and seroconversion, treatment failure and virological breakthrough. Treatment failure was defined as completion of at least 24 weeks of treatment without two consecutive measurements of serum HBV DNA $<5\log_{10}$ copies/ml. Virological breakthrough was defined as a persistent (two consecutive determinations) on-treatment increase in HBV DNA of $>1\log_{10}$ above nadir (9).

The incidence of adverse events (AEs), serious adverse events (SAEs), death and graded laboratory abnormalities was analysed during the study visits.

Genotypic resistance analysis

Hepatitis B virus DNA was amplified by PCR (COBAS Amplicor HBV Monitor^{TM} assay, Roche Molecular Systems, Branchburg, NJ, USA; lower limit of detection of 300 copies/ml) for all the serum samples collected at screening and at Week 48 from patients with '1 $\log_{10}$ above nadir' virological breakthrough, the 344-codon reverse transcriptase domain of the HBV polymerase gene was sequenced at an independent laboratory (Delft diagnostic laboratory, Fonteijinenburghlaan 5, 2275 CX, Voorburg, the Netherlands). This automated method has been reported previously and detects potential resistance mutations that comprise at least 25% of the amplified viral DNA (10, 11).

Data analysis

This study was powered for treatment differences on the primary endpoint. This design was based on the phase IIb study results (9) and a $1\log_{10}$ copies/ml increment in serum HBV DNA reduction (primary endpoint) was expected at Week 24. With these assumptions and an estimated drop-out rate of 10%, a sample size of 240 patients (120 patients per-treatment) provided >90% power for the primary comparison of HBV DNA reduction at Week 24, and approximately 85% for the comparison of ALT normalization.

Two analysis populations were defined for this study. All randomized patients who received at least one dose of the study medication and those who had at least one observation after baseline were included in the intent-to-treat (ITT) population. These patients were used for analysing all efficacy endpoints. The last observation carried forward approach was applied for missing values.

Primary efficacy variables were analysed by ANCOVA. The continuous and categorical variables were compared by the two-sided *t*-test and the χ^2 testing respectively. Descriptive statistics for secondary endpoints including serum HBV DNA levels, change from the baseline in serum HBV DNA and serum ALT concentrations, was presented by visit and treatment group. Treatment failure and virological breakthrough were analysed using an ANCOVA model with effects for baseline stratification factors (HBeAg-negative vs. -positive status, 12–24 vs. 25–52 weeks of prior lamivudine therapy), at the 0.05 significance level. The Cochran–Mantel–Haenszel method was used to combine stratified subgroups for testing response rates between the treatment groups.

McNemar's test was used to determine the significance for emergence of mutations at each of the 344 residues across all breakthrough patients. The safety population consisted of all patients who received at least one dose of the study medication with at least one post-baseline

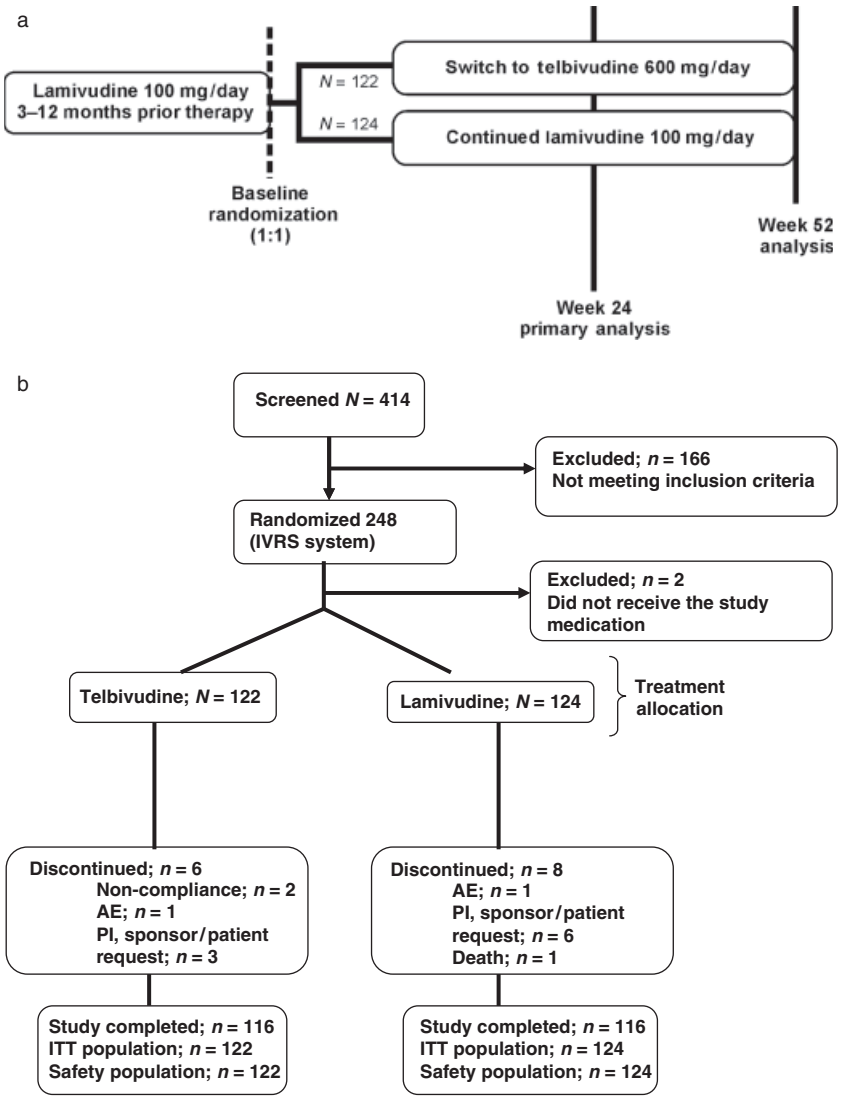

Fig. 1. (a) Trial design – Laboratory evaluations were conducted at screening, at baseline (randomization) and at Weeks 2, 4, 8, 12, 16, 24, 32, 40, 48 and 52. During each visit HBeAg, HBeAb, HBsAg and HBsAb were assayed at the central reference laboratory using standard, commercially available enzyme immunoassays. Serum HBV DNA levels were quantified by the COBAS Amplicor HBV Monitor Assay. Complete physical examination was performed at screening, Week 24 and Week 52 (study end). Additional physical examinations were performed at visits whenever deemed necessary. (b) Flow chart representing patient disposition. AE, adverse event; HBV, hepatitis B virus; ITT, intent to treat.

observation. For all analyses based on the safety population, patients were analysed according to the treatment received. The incidence of AEs and frequency of Grade 3 or 4 laboratory abnormalities were summarized by treatment groups and compared with Fisher's exact test.

Results

Patients

Of 414 screened patients, 248 fulfilled the inclusion criteria and were randomized; the ITT population comprised 246 patients receiving telbivudine ($n = 122$) or lamivudine ($n = 124$). On treatment, 116 patients in each group completed this study (Fig. 1b). Baseline demographics and disease characteristics were similar among patients in both groups (Table 1). The number of HBeAg-positive patients was equal ($n = 81$) for both treatment groups. There were 41 telbivudine- and 43 lamivudine-treated patients who were HBeAg-negative.

Serum HBV DNA samples collected at screening from 246 ITT patients (122 telbivudine; 124 lamivudine) were sequenced with complete sequence data obtained from 223 patients. Samples that could not be amplified were presumed to carry the wild-type sequence. Overall, 15.9% patients [39/246 of the serum samples; 21/122 (17.2%) and 18/124 (14.5%) in the telbivudine and lamivudine groups respectively] carried one of M204 mutations (I, V, or mixed). There was no significant

difference in the prevalence of pre-existing lamivudine-resistant mutations between treatment groups.

Efficacy results in the intent-to-treat population

Significantly ($P < 0.001$) greater reduction in serum HBV DNA levels from baseline at Week 24 (primary endpoint) was seen with telbivudine (mean Δ -1.9 ± 0.18; mean serum HBV DNA levels $3.8 \pm 0.19 \log_{10}$ copies/ml) compared with lamivudine treatment (mean Δ -0.9 ± 0.27, mean serum HBV DNA levels $5.1 \pm 0.26 \log_{10}$ copies/ml).

The percent of patients experiencing undetectable HBV DNA levels, HBeAg loss and seroconversion at Week 24 was higher in the telbivudine group. None of the patients in either group had HBsAg loss or seroconversion while numerically higher rates of ALT normalization were achieved in lamivudine patients (Table 2).

The greater decline in serum HBV DNA levels in telbivudine group was retained at all timepoints from Week 24 onwards (mean HBV DNA levels not shown) until Week 52 although serum HBV DNA levels increased at Week 52 in both telbivudine and lamivudine group (Table 2).

At Week 52, telbivudine treatment resulted in significantly higher rates of undetectable serum HBV DNA (46%) compared with lamivudine 31% ($P = 0.005$). The proportion of patients with ALT normalization was higher in the telbivudine group (60%) compared with the lamivudine group (51%).

Table 1. Demographical and baseline disease characteristics (intent-to-treat population)

Baseline patient characteristics	Telbivudine $N = 122$	Lamivudine $N = 124$
Age in years – mean (SE)	35.5 (1.0)	37.3 (1.0)
Weight in kg – mean (SE)	71.2 (1.5)	71.5 (1.24)
Height in cm – mean (SE)	169.7 (0.8)	170.4 (0.7)
Gender – *n* (%) male	90 (74)	96 (77)
Race – *n* (%)		
Caucasians	15 (12)	13 (10)
Asians	75 (61)	76 (61)
Chinese	55 (68)	63 (80)
Korean	13 (16)	12 (15)
African/African-Americans	0 (0)	2 (2)
Middle Eastern/Indians	25 (20)	29 (23)
Others	7 (6)	4 (3)
HBeAg status		
HBeAg-positive	81 (66)	81 (65)
HBeAg-negative	41 (34)	43 (35)
Serum HBV DNA ($\log_{10}$ copies/ml),		
Mean (SE)	5.6 (0.21)	6.0 (0.24)
Median	5.0	5.3
Serum ALT concentration (IU/L)		
Mean (SE)	68.5 (7.1)	57.7 (4.8)
Median	41.5	40.5
Duration of prior lamivudine-therapy (years)		
Mean (SE)	0.6 (0.03)	0.5 (0.03)
Median	0.5	0.4

P-values for continuous variables are from a two-sided *t*-test. *P*-values for categorical variables are from a χ^2 test. Percentages are based on the number of patients with non-missing data for the parameter in each treatment group.

ALT, alanine transferase ; HBV, hepatitis B virus; SE, standard error.

Efficacy results by HBeAg status and duration of prior lamivudine treatment

HBeAg-positive patients switched to telbivudine had better outcomes compared with the group of continued lamivudine treatment at all timepoints, with significantly higher HBV DNA decline and rate of HBV DNA undetectable at Week 52 ($P < 0.05$) regardless of the duration of prior lamivudine treatment. However, those who were switched to telbivudine treatment post-lamivudine exposure (< 24 week) retained benefits of greater decline in serum HBV DNA levels and higher rates of HBV DNA undetectable at Week 52 similar to that observed at Week 24 (Table 3). The outcomes for HBeAg-negative patients at Week 24 were generally better but no significant differences were observed because of the small number of patients in this group.

Table 2. Efficacy results with or telbivudine- or lamivudine-treatment at Week 24 and Week 52 (intent-to-treat population, last observation carried forward)

	Week 24			Week 52		
Efficacy parameter	Telbivudine $N = 122$	Lamivudine $N = 124$	*P*-values	Telbivudine $N = 122$	Lamivudine $N = 124$	*P*-values
Serum HBV DNA [$\log_{10}$ copies/ml] – mean (SE)	3.8 (0.19)	5.1 (0.26)	< 0.001	4.2 (0.25)	5.9 (0.30)	< 0.001
HBV DNA undetectable – *n*/*N* (%)	49/121 (40)	39/124 (31)	0.097	56/121 (46)	38/124 (31)	0.005
HBV DNA change from baseline ($\log_{10}$ copies/ml) – mean (SE)	− 1.9 (0.18)	− 0.9 (0.27)	< 0.001	− 1.5 (0.28)	− 0.1 (0.31)	< 0.001
HBeAg loss – *n*/*N* (%)	8/81 (10)	7/81 (9)	0.569	15/81 (19)	11/81 (14)	0.277
HBeAg seroconversion – *n*/*N* (%)	8/81 (10)	6/81 (7)	0.364	12/81 (15)	8/81 (10)	0.095
ALT normalization – *n*/*N* (%)	26/53 (49)	36/53 (68)	0.067	32/53 (60)	27/53 (51)	0.202
Treatment failure – *n*/*N* (%)	–	–	–	6/122 (5)	25/124 (20)	< 0.001

P-values are from a CMH χ^2 test for discrete parameters and from ANCOVA for continuous parameters.

CMH, Cochran–Mantel–Haenszel; HBV, hepatitis B virus.

Table 3. Efficacy results at Week 24 and Week 52 with telbivudine or lamivudine stratified by HBeAg status and duration of prior lamivudine treatment (intent-to-treat population)

	Week 24		Week 52		
HBeAg status, duration of prior lamivudine treatment	Change from baseline in serum HBV DNA Mean+SE	Undetectable HBV DNA *n'/N* (%)	Change from baseline in serum HBV DNA Mean+SE	Undetectable HBV DNA *n'/N* (%)	
Positive, 12–24 weeks (telbivudine; *N* = 42, lamivudine; *N* = 43)	− 2.419 ± 0.315	− 2.211 ± 0.513	11/42 (26)	13/43 (30)	− 2.348 ± 0.464*	− 1.103 ± 0.627	19/42 (45)*	10/43 (23)
Positive, 25–52 weeks (telbivudine; *N* = 39, lamivudine; *N* = 39)	− 1.235 ± 0.336	0.483 ± 0.373	10/39 (26)	2/39 (5)	− 0.280 ± 0.509**	1.502 ± 0.407	9/39 (23)*	2/39 (5)
Negative, 12–24 weeks (telbivudine; *N* = 29, lamivudine; *N* = 28)	− 2.290 ± 0.366	− 1.004 ± 0.497	21/28 (75)	17/28 (61)	− 1.938 ± 0.518	− 0.777 ± 0.573	23/28 (82)	19/28 (68)
Negative, 25–52 weeks (telbivudine; *N* = 12, lamivudine; *N* = 14)	− 1.298 ± 0.360	− 0.513 ± 0.579	7/12 (58)	7/14 (50)	− 1.231 ± 0.750	0.014 ± 0.660	5/12 (42)	7/14 (50)

*$P = 0.002$ telbivudine vs. lamivudine.
**$P < 0.05$ telbivudine vs. lamivudine. Percentages are based on the number of patients in each treatment group eligible for meeting the endpoint (*n'*).
HBV, hepatitis B virus.

Treatment failure and association with pre-existing genotypic resistance

At Week 52, the overall rate of treatment failure was significantly lower in telbivudine patients (5%; 6/122 patients) than in lamivudine patients (20%; 25/124 patients, $P < 0.001$). Treatment failure was most frequently associated with the presence of pre-existent genotypic resistance mutations at screening in telbivudine patients (83%; 5/6 patients) than in lamivudine patients (52%; 13/25 patients) (Table 4). Among the five telbivudine patients with pre-existing M204 resistance mutations who experienced treatment failure, three had the M204I telbivudine signature mutation and one carried the M204V mutation with the other one being a mixed M204M/I at screening. Retrospectively, half of the telbivudine patients (3/6, 50%) with a pre-existing M204I mutation experienced treatment failure, compared with only one of the eight patients (1/8, 12%) with a pre-existing M204V, including mixed mutations.

Incidences of treatment failure by HBeAg status related to prior duration of lamivudine treatment

The duration of prior lamivudine therapy was predictive of the probability of consecutive treatment failure. One (1%) of the patients in the telbivudine switch group with <24 weeks of prior lamivudine therapy experienced treatment failure compared with three patients (4%) in the lamivudine group. The rate of treatment failure was lower in HBeAg-positive patients who switched to telbivudine and had >24 weeks of prior lamivudine treatment (10%; 4/39 patients) compared with those continuing lamivudine (51%; 20/39 patients). A similar trend was seen in HBeAg-negative patients who switched to telbivudine and had >24 weeks of prior lamivudine treatment (telbivudine: 8%; 1/12 patients and lamivudine: 14%; 2/14 patients). In both treatment groups, the rates of treatment failure increased substantially with a longer duration (>24 weeks) of prior lamivudine treatment (Table 4).

Virological breakthrough and genotypic resistance

Overall virological breakthrough assessed at 48 weeks was similar in telbivudine and lamivudine groups, 15 vs. 16% (telbivudine: 15 HBeAg positive and three HBeAg negative out of 122 patients; lamivudine: 15 HBeAg positive and five HBeAg negative out of 124 patients) (Table 5). When the duration of prior lamivudine exposure was considered, virological breakthrough in the telbivudine switch group with 12–24 weeks of prior lamivudine treatment was lower than in the group of continued lamivudine (7 vs. 18%). In contrast, for a longer lamivudine exposure, virological breakthrough in the telbivudine switch group was higher than in patients who continued on lamivudine (25 vs. 13%).

Genotypic resistance at the M204 codon appeared in 15/18 (83.3%) telbivudine and 13/20 lamivudine

Table 4. Treatment failure and the presence of pre-existing genotypic resistance at Week 52, stratified by HBeAg status and the duration of prior lamivudine therapy (intent-to-treat population)

	Telbivudine $N = 122$		Lamivudine $N = 124$	
HBeAg status, duration of prior lamivudine treatment	TF n'/N (%)	Pre-existing genotyping resistance in TF patients n'/N (%)	TF n'/N (%)	Pre-existing genotyping resistance in TF patients n'/N (%)
Positive, 12–24 weeks (telbivudine; $N = 42$, lamivudine; $N = 43$)	1/42 (2.4)	0/42 (0)	3/43 (7)	1/43 (2.3)
Negative, 12–24 weeks (telbivudine; $N = 29$, lamivudine; $N = 28$)	0/29 (0)	0/29 (0)	0/28 (0)	0/28 (0)
Combined 12–24 weeks (A)	1/71 (1.4)	0/71 (0)	3/71 (4.2)	1/71 (1.4)
Positive, 25–52 weeks (telbivudine; $N = 39$, lamivudine; $N = 39$)	4/39 (10.3)	4/39 (10.2)	20/39 (51.3)	11/39 (28.2)
Negative, 25–52 weeks (telbivudine; $N = 12$, lamivudine; $N = 14$)	1/12 (8.3)	1/12 (8.3)	2/14 (14.3)	1/14 (7.1)
Combined 25–52 weeks (B)	5/51 (9.8)	5/51 (9.8)	22/53 (41.5)	12/53 (22.6)
Total (A+B)	6/122 (4.9)	5/122 (4.1)	25/124 (20.2)	13/124 (10.5)

Percentages are based on the number of patients in each treatment group eligible for meeting the endpoint (n').
TF, treatment failure.

Table 5. Virological breakthrough and genotypic resistance at Week 48 stratified by the duration of prior lamivudine therapy (all patients and patients with wild-type HBV virus at screen)

	Telbivudine $N = 122$		Lamivudine $N = 124$	
Duration of prior lamivudine treatment	1 $\log_{10}$ above nadir VB n'/N (%)	Genotypic resistance n'/N (%)	1 $\log_{10}$ above nadir VB n'/N (%)	Genotypic resistance n'/N (%)
All patients				
12–24 weeks	5/71 (7.0)	5/71 (7.0)	13/71 (18.3)	9/71 (12.7)
24–52 weeks	13/51 (25.4)	10/51 (19.67)	7/53 (13.2)	4/53 (7.5)
Combined	18/122 (14.8)	15/101 (12.3)	20/124 (16.1)	13/124 (10.5)
Patients with wild-type HBV virus at screen				
12—24 weeks	5/58 (8.6)	5/58 (8.6)	13/67 (19.4)	9/67 (13.4)
24–52 weeks	8/43 (18.6)	7/43 (16.3)	6/39 (15.4)	4/43 (10.3)
Combined	13/101 (12.9)	12/101 (11.9)	19/106 (17.9)	13/106 (12.3)

Percentages are based on the number of patients in each treatment group eligible for meeting the endpoint (n').
HBV, hepatitis B virus; VB, virological breakthrough.

breakthrough patients. Of the 18 telbivudine breakthrough patients, two (11%) carried M204 mutations (one M204V, one M204I) at screening that persisted post-breakthrough and therefore were not treatment related. In 15/18 (83.3%) telbivudine breakthrough patients, the M204I signature mutation emerged while on treatment, with 14/15 (93%) categorized as a pure M204I mutant and one as a mixed mutant population (M204M/I/V). Interestingly, one patient with a treatment-emergent M204I mutation was genotyped as M204V at screening but M204I at Week 48. The remaining telbivudine breakthrough patients carried a wild-type M204 and no other known resistance mutation at Week 48; this breakthrough may reflect a lack of compliance. Despite the prior lamivudine exposure, no treatment-emergent M204V change (including the M204V-L180M double mutant) was seen in response to telbivudine therapy in this study. No novel primary resistance mutation was identified in telbivudine breakthrough patients.

Of the 20 breakthrough lamivudine patients, 13 (65%) exhibited treatment-emergent codon M204 genotypic changes [M204I (54%), M204V (15%)], and L180M or L801/V secondary mutations. A single lamivudine patient possessed the M204I resistance strain at both screening and Week 48 and was therefore excluded from the subsequent analysis of treatment-emergent mutations. The final six lamivudine patients had HBV genomes with wild-type M204 codons despite the viral rebound, presumably related to non-compliance or a loss of response to lamivudine for reasons unrelated to genotypic resistance.

The rates of the virological breakthrough and genotypic resistance were also calculated excluding patients with pre-existing mutations and considering only those

who carried wild-type HBV viruses at screening (Table 5). In patients with wild-type virus at screening, the virological breakthrough was lower in telbivudine switch (13%) compared with continued lamivudine group (18%) and similar to the overall study population (15%). Considering the duration of lamivudine exposure in these patients, the rate of viral breakthrough in telbivudine switch patients with longer (24–52 weeks) lamivudine exposure was 18%, which was lower than in the analogous group of overall population (25%) and suggest that the mutations developed during prolonged lamivudine exposure could have confounded the benefit of telbivudine switch.

Safety and adverse events

Both treatments were well tolerated with the incidence of AEs throughout Week 52 similar. Sixteen patients in the telbivudine group (13%) and 20 patients in the lamivudine group (16%) experienced drug-related AEs (Table 6). Nine percent of patients ($n = 21$) experienced a post-baseline, on-treatment, Grade 3 or 4 laboratory abnormality. There were four patients with investigator-described myalgia (lamivudine, $n = 1$ and telbivudine, $n = 3$). Three of these patients experienced Grade 1 AE of myalgia (lamivudine, $n = 1$ and telbivudine, $n = 2$) but recovered spontaneously. In one case, the investigator considered the event to be reasonably or possibly related to the study drug (lamivudine, $n = 1$). The incidences of ALT elevation were similar between treatment groups (telbivudine, 2%; lamivudine, 3%) and were considered unrelated to the study drug.

Overall, SAEs occurred in five (4%) and eight (6%) of the telbivudine and lamivudine patients, respectively, including myocardial infarction and haemorrhoids. None of the SAEs was study drug related in either treatment group.

Table 6. On-treatment adverse events by preferred term in decreasing frequency occurring in ≥4% of patients in either treatment group

Adverse events	Telbivudine $N = 122$ n (%)	Lamivudine $N = 124$ n (%)
Upper respiratory tract infection	9 (7)	10 (8)
Headache	9 (7)	8 (6)
Nasophyrangitis	7 (6)	6 (5)
Cough	6 (5)	3 (2)
Abdominal pain	5 (4)	7 (6)
Arthralgia	5 (4)	5 (4)
Nausea	5 (4)	1 (< 1)
Pharyngolaryngeal pain	5 (4)	4 (3)
ALT increased	4 (3)	6 (5)
Fatigue	4 (3)	7 (6)
Diarrhoea	3 (2)	6 (5)
Hepatic enzyme increased	3 (2)	5 (4)

Percentages are based on the number of patients in the safety population in each treatment group.
ALT, alanine transferase.

Discussion

The primary goal of antiviral therapy for CHB is an early and durable suppression of HBV replication with the ultimate goal of preventing advanced liver sequelae (cirrhosis and HCC). Lamivudine, the first oral anti-HBV agent is still the number one prescribed drug worldwide for treatment of CHB. However, a major problem with lamivudine therapy is the frequent emergence of drug resistance mutations, most commonly located in the YMDD motif at position rt204 (M204V/I) either with or without the compensatory mutations at position rt180 (L180M) and rt173 (V173L) (12). During the first year of lamivudine therapy, 15–30% patients fail to develop durable virological response because of emergence of HBV strains resistant to lamivudine (7). It was demonstrated that the evolution of lamivudine-resistant HBV leading to suboptimal efficacy is inversely proportional to the degree of HBV DNA suppression during early treatment (13). While some patients with YMDD mutant HBV may maintain low levels of viraemia on lamivudine, such patients commonly develop variable return of HBV replication, high viraemia, and variably elevated serum ALT levels (14, 15). Initially considered no more than a virological problem, lamivudine resistance is now recognized to be a relevant clinical problem, which requires specific therapeutic management (7). At the time this study was planned one of proposed strategies for treatment of CHB patients with suboptimal response to an oral antiviral was a switch to a more potent drug. Based on this hypothesis and the superior efficacy of telbivudine over lamivudine shown in the GLOBE trial (8), the present study aimed to define the benefit of switching patients who remained viraemic under lamivudine treatment to telbivudine.

While the duration of prior lamivudine therapy for switching to other treatment is difficult to define, at the time of inception of this trial the best strategy was to select the patients based on active CHB (serum HBV DNA level $>3 \log_{10}$ copies/ml) with major ALT elevation (particularly ALT $>5 \times$ ULN) for a duration of 1 year or less (16). Other simultaneous ongoing trials used a similar design.

Results of this study are consistent with GLOBE (8, 17) and other studies for telbivudine-treated patients, in achieving significantly greater reductions in HBV DNA levels and PCR undetectability at Weeks 24 and 52 compared with lamivudine-treated patients. An early switch to telbivudine in patients with prior lamivudine exposure demonstrated a significantly lower rate of treatment failure. In the majority of telbivudine switch patients (83.3%), treatment failure was associated with pre-existing M204 lamivudine resistance mutations at screen compared with only about half (56%) in the lamivudine continuing group. Interestingly, the M204I

signature mutation was characterized in half of the telbivudine patients with pre-existing M204 resistance mutations who experienced treatment failure.

Even in patients classified as carrying wild-type HBV at screening, the rates of virological breakthrough and genotypic resistance for telbivudine at Week 48 in this study were higher than the rates found in treatment-naïve patients in the pivotal GLOBE study (17). This difference may be attributed to the fact that genotypic resistance analysis was performed at screening and not at baseline leaving a gap of 6 weeks when resistance mutations may have developed but were not detected. Another explanation may be that owing to the lower sensitivity of the mutation assay there were some lamivudine mutations that were not detected. In the GLOBE study, the signature mutation associated with telbivudine resistance was M204I, found either alone or in association with the secondary mutations L80I/V or L180M, findings that were confirmed in the present study (8).

Interpretation of these results needs to take into account that this study was designed based on the superior efficacy and lower resistance rates to telbivudine as compared with lamivudine in the overall HBV population and that the resistance profile to telbivudine and cross resistance to lamivudine and telbivudine was not fully established when this study started. Lamivudine-experienced patients enrolled in this study, therefore, included a broader population not stratified according to pre-existing lamivudine resistance, which today is known to be an important criterion to decide the success of switching therapies in CHB patients. Lamivudine-experienced patients were (1) viraemic patients on lamivudine therapy carrying established lamivudine resistance or wild-type HBV strain at screen, and (2) those successfully achieving viral suppression or maintaining persistent viral load $<10^3$ copies/ml on lamivudine therapy. The mixed data for telbivudine in patients with established lamivudine resistance from the current study have been recently updated in specific product characteristic for telbivudine that does give a clear recommendation as to not use telbivudine to treat patients carrying established lamivudine resistance, while there are currently no published data for patients with successful evolution of CHB during lamivudine therapy and switching to telbivudine. According to international treatment guidelines for CHB patients, it is important to identify HBV-resistance mutations before formulating a regimen and in case of established resistance mutation adding rather than switching to a more potent drug that does not share cross resistance. For this population, the combination of lamivudine or telbivudine with advefovir or tenefovir, might have been a better option, although this was not evident at the time of the inception of this study. Nevertheless, in the absence of stratification based on pre-existing lamivudine resistance, these results clearly indicate that the duration of prior lamivudine exposure was a major determinant of better virological outcome in telbivudine switch patients with persistent viral replication under lamivudine treatment – the increased power of lamivudine-resistance mutations with each additional month of ongoing treatment is well known. Only one patient with <24 weeks of lamivudine exposure who was switched to telbivudine experienced treatment failure and the rates of virological breakthrough and genotypic resistance were lower compared with the patients continuing lamivudine therapy. In contrast, in both groups the rates of treatment failure, virological breakthrough and genotypic resistance increased substantially in relation to longer duration (>24 weeks) of prior lamivudine exposure. Hence, it appears that early (≤ 24 weeks) switch to telbivudine may benefit patients who remain viraemic under lamivudine treatment.

Both treatments were well tolerated and showed a similar safety profile as observed in the GLOBE study (8). Patients who switched to telbivudine from lamivudine did not experience any additional spectrum of adverse effects.

In conclusion, this study shows that early switch (before 24 weeks of lamivudine treatment) to telbivudine may improve the patient's outcomes. Switching lamivudine-resistant patients to telbivudine monotherapy may have a limited role, and to achieve a more potent antiviral effect and prevent multidrug resistance, the combination of telbivudine with another nucleotide could be another option.

Acknowledgements

The authors wish to thank the patients and study centres for participating in this study. The authors wish to thank Mechthild Jung, PhD, Vijay Singh, PhD and Charles Koehne, MSc for their editorial support in the preparation of this manuscript.

References

1. Gaeta GB, Stornaiuolo G. Therapy of chronic hepatitis B: focus on telbivudine. *Dig Liver Dis* 2007; **39**: S372–8.
2. Iloeje UH, Yang HI, Jen CL, *et al*. Risk and predictors of mortality associated with chronic hepatitis B infection. *Clin Gastroenterol Hepatol* 2007; **5**: 921–31.
3. Iloeje UH, Yang HI, Su J, *et al*. Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. *Gastroenterology* 2006; **130**: 678–86.
4. Chen G, Lin W, Shen F, *et al*. Past HBV viral load as predictor of mortality and morbidity from HCC and chronic liver disease in a prospective study. *Am J Gastroenterol* 2006; **101**: 1797–803.
5. Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology* 2009; **50**: 661–2.
6. Ferir G, Kaptein S, Neyts J, De Clercq E. Antiviral treatment of chronic hepatitis B virus infections: the past, the present and the future. *Rev Med Virol* 2008; **18**: 19–34.
7. Lampertico P, Vigano M, Colombo M. Management of lamivudine resistance: an overview. *Hepatitis B Annu* 2008; **5**: 66–80.

8. Liaw YF, Gane E, Leung N, *et al.* 2-year GLOBE trial results: telbivudine is superior to lamivudine in patients with chronic hepatitis B. *Gastroenterology* 2009; **136**: 486–95.
9. Lai CL, Leung N, Teo EK, *et al.* A 1-year trial of telbivudine, lamivudine, and the combination in patients with hepatitis B e antigen-positive chronic hepatitis B. *Gastroenterology* 2005; **129**: 528–36.
10. Marcellin P, Lau GK, Bonino F, *et al.* Peginterferon alfa-2a alone, lamivudine alone, and the two in combination in patients with HBeAg-negative chronic hepatitis B. *N Engl J Med* 2004; **351**: 1206–17.
11. Lau GK, Piratvisuth T, Luo KX, *et al.* Peginterferon alfa-2a, lamivudine, and the combination for HBeAg-positive chronic hepatitis B. *N Engl J Med* 2005; **352**: 2682–95.
12. Libbrecht E, Doutreloigne J, Van De Velde H, *et al.* Evolution of primary and compensatory lamivudine resistance mutations in chronic hepatitis B virus-infected patients during long-term lamivudine treatment, assessed by a line probe assay. *J Clin Microbiol* 2007; **45**: 3935–41.
13. Kurashige N, Hiramatsu N, Ohkawa K, *et al.* Initial viral response is the most powerful predictor of the emergence of YMDD mutant virus in chronic hepatitis B patients treated with lamivudine. *Hepatol Res* 2008; **38**: 450–6.
14. Liaw YF, Leung NW, Chang TT, *et al.* Effects of extended lamivudine therapy in Asian patients with chronic hepatitis B. Asia hepatitis lamivudine study group. *Gastroenterology* 2000; **119**: 172–80.
15. Leung NWY, Lai CL, Chang TT, *et al.* Three year lamivudine therapy in chronic HBV. *J Hepatology* 1999; **30**: 59, Abstract (GS5/25).
16. Leung N. Treatment of chronic hepatitis B: case selection and duration of therapy. *J Gastroenterol Hepatol* 2002; **17**: 409–14.
17. Lai CL, Gane E, Liaw YF, *et al.* Telbivudine versus lamivudine in patients with chronic hepatitis B. *N Engl J Med* 2007; **357**: 2576–88.