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Baseline characteristics and early on-treatment response predict the outcomes of 2 years of telbivudine treatment of chronic hepatitis B☆

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See Editorial, pages 1–3

***Background/Aims*: In the GLOBE trial, telbivudine treatment was identified as a significant, independent predictor of better outcomes at 2 years. We analyzed all telbivudine recipients in this trial to determine the predictors of optimal outcomes.**

***Methods*: The intent-to-treat population comprised 458 HBeAg-positive and 222 HBeAg-negative telbivudine-treated patients. Multivariate logistic regression analyses were employed to evaluate baseline and/or early on-treatment variables.**

***Results*: Baseline HBV DNA < 9 $\log_{10}$ copies/mL, or ALT levels $\geqslant 2\times$ above normal were strong pretreatment predictors for HBeAg-positive, but not for HBeAg-negative patients. However, non-detectable serum HBV DNA at treatment week 24 (TW24) was the strongest predictor for better outcomes for both groups. A combination of pretreatment characteristics plus TW24 response identified subgroups with the best outcomes: (1) HBeAg-positive patients with baseline HBV DNA < 9 $\log_{10}$ copies/mL, ALT $\geqslant 2\times$ above normal and non-detectable HBV DNA at TW24 achieved at 2 years: non-detectable HBV DNA in 89%, HBeAg seroconversion in 52%, telbivudine resistance in 1.8%; and (2) HBeAg-negative patients with baseline HBV DNA < 7 $\log_{10}$ copies/mL and non-detectable serum HBV DNA at TW24 achieved at 2 years: non-detectable HBV DNA in 91%, telbivudine resistance in 2.3%.**

***Conclusion*: During telbivudine treatment, non-detectable serum HBV DNA at treatment week 24 is the strongest predictor for optimal outcomes at 2 years.**

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1. Introduction

Treatment of patients with chronic hepatitis B is evolving rapidly with an increasing range of treatment options, the wider use of molecular diagnostic assays, as well as accumulating data from longer-term antiviral therapy. Profound and long-lasting suppression of HBV replication, either maintained on-therapy or sustained after stopping therapy, has been identified as the key determinant to achieve the goals of therapy – to reduce liver damage, to prevent development of cirrhosis and/or hepatocellular carcinoma [1]. In patients with HBeAg-positive chronic hepatitis B, HBeAg seroconversion has been established as a key surrogate marker of treatment response, associated with improved clinical outcomes [2,3]. According to current guidelines, antiviral treatment is recommended for HBeAg-positive patients with serum ALT levels $\geqslant 2$ times the upper limit of normal ($\times$ULN), while in patients with HBeAg-negative chronic hepatitis B treatment initiation depends on HBV DNA levels together with either serum ALT $\geqslant 2$ $\times$ULN, or liver histology showing advanced liver disease in patients with normal or minimally raised serum ALT levels [4–7].

Analyses of patients' characteristics before treatment with interferon identified high serum ALT, low HBV DNA levels and high necro-inflammation grade on liver biopsy as predictive of higher rates of HBeAg seroconversion [8–12]. Increased pretreatment ALT levels were also predictive of a higher probability of HBeAg loss after 1 year of treatment with lamivudine, which was similar for both Asian and Caucasian patients [13]. Importantly, patients differ not only in their pretreatment profile, but also in their on-treatment response. Regular monitoring of HBV DNA levels during treatment is crucial for optimal management of patients [7], as it allows to check for efficacy and compliance, as well as to modify therapy for those with suboptimal responses. A significant correlation has been found between serum HBV DNA levels at mid-treatment and the outcome of interferon therapy [14,15]. The degree of viral suppression with oral antivirals has also been associated with subsequent efficacy outcomes and may be a useful marker in the clinical practice [16–20]. On-treatment assessment of the early virologic response, with treatment adjustment to maximize HBV suppression in patients with a suboptimal early response – the "roadmap" concept has been proposed as a strategy to improve long-term treatment results [21]. However, previous trials of anti-HBV therapy have provided only limited information to evaluate the importance of pretreatment characteristics vs. the early on-treatment response in predicting the long-term treatment outcomes. Moreover, no study reported to date has analyzed the predictors of treatment response after more than 1 year of therapy with an oral antiviral agent in an intent-to-treat population.

The GLOBE trial, the largest trial in chronic hepatitis B, demonstrated that telbivudine is superior to lamivudine for all efficacy measures over 2 years of therapy [17,22]. Logistic regression analyses identified telbivudine treatment along with serum HBV DNA levels – at baseline or at treatment week 24, as significant independent predictors of better outcomes at 2 years [22]. In this study we extended the multivariate analyses by including all pretreatment patients' characteristics and the early on-treatment responses (treatment week 12 or 24) and evaluated their impact alone and in combination to identify the strongest predictor for optimal outcomes of 2 years treatment with telbivudine.

2. Methods

2.1. Patients

The GLOBE trial involved 921 HBeAg-positive and 446 HBeAg-negative patients, as reported previously [17,22]. The intent-to-treat population of telbivudine-treated participants comprised 458 HBeAg-positive and 222 HBeAg-negative patients (Table 1). Based on the pre-specified analysis plan, 37 telbivudine-treated patients discontinued treatment due to efficacy (achieved HBeAg seroconversion) before week 104. A total of 56 (8%) telbivudine recipients withdrew prior to 2 years because of non-compliance ($n = 8$); pregnancy ($n = 4$); adverse event ($n = 5$); lack of efficacy after week 24 ($n = 6$); or patient/investigator or sponsor request ($n = 33$). In the intent-to-treat analyses all patients who discontinued telbivudine for reasons other than efficacy were considered to have failed the endpoints.

Standardized tests were performed centrally by Quintiles Transnational (Research Triangle Park, NC). Serum HBV DNA was quantified by COBAS® Amplicor HBV Monitor polymerase chain reaction (PCR) assay (Roche Molecular Systems; detection limit 300 copies/mL). Informed consent was obtained from each patient enrolled in the study. The study was conducted in compliance with the Declaration of Helsinki and in accordance with Good Clinical Practice guidelines and local regulations.

2.2. Study endpoints

The present analyses focused on key therapeutic endpoints at 2 years, including proportions of patients with non-detectable serum HBV DNA, serum ALT normalization, HBeAg seroconversion and telbivudine resistance. As reported previously, resistance was defined as emergence of treatment-associated resistance mutations, identified

Table 1
Demographics and baseline characteristics of telbivudine-treated patients in the GLOBE trial (intent-to-treat population).

N	HBeAg-positive 458	HBeAg-negative 222
Age: mean years (range)	32 (16–63)	43 (17–68)
Male gender: number (%)	333 (73)	174 (78)
Weight: mean kg (range)	66 (38–126)	72 (42–123)
Race or ethnic group: number (%)		
Chinese	265 (58)	116 (52)
Non-Chinese Asian	115 (25)	29 (13)
White	52 (11)	46 (21)
Black	4 (1)	3 (1)
Latino	2 (<1)	2 (1)
Middle Eastern/Indian	8 (2)	6 (3)
Other	12 (3)	20 (9)
HBV genotype: number (%)		
A	24 (5)	12 (5.4)
B	129 (28)	59 (26.6)
C	259 (57)	89 (40.1)
D	42 (9)	57 (25.7)
Other or unknown	4 (1)	5 (2.3)
Serum ALT (IU/L)		
Means ± SE	146.2 ± 5.36	137.0 ± 6.94
Median (range)	110.5 (19–1137)	99.0 (31–569)
Serum HBV DNA ($\log_{10}$ copies/mL)		
Means ± SE	9.5 ± 0.09	7.7 ± 0.12
Median (range)	9.6 (3.8–16.0)	7.2 (3.0–13.0)
Liver histology: mean values		
Total Knodell HAI score	8.9	9
Knodell necroinflammatory score	7.4	7.3
Ishak fibrosis score	2.1	2.3

by direct sequencing of the amplified HBV DNA at baseline and from sera of all patients with serum HBV DNA > 3 $\log_{10}$ copies/mL at week 104 [22]. Viral breakthrough was defined as persistent (two consecutive determinations) on-treatment increase of serum HBV DNA > 1 $\log_{10}$ copies/mL above nadir level [23].

2.3. Statistical analysis

All telbivudine-treated patients were considered for the analyses in the present study. Pre-specified analyses were undertaken to assess relationships between early antiviral responses and outcomes at 2 years that included the proportions of patients with non-detectable serum HBV DNA by PCR, HBeAg seroconversion, ALT normalization and resistance. Patients were categorized in four groups according to serum HBV DNA level at treatment week 12 and 24: (i) PCR-negative; (ii) detectable but <3 $\log_{10}$ copies/mL; (iii) from 3 to <4 $\log_{10}$ copies/mL; and (iv) ⩾4 $\log_{10}$ copies/mL. Baseline ALT levels were categorized into three groups: <2 ×ULN, 2–5 ×ULN and >5 ×ULN, as previously published [13,24]. Stepwise logistic regression analyses were performed to identify variables associated with treatment outcomes. Baseline variables included in the model were age, gender, BMI, ALT, Ishak fibrosis score, serum HBV DNA level, Knodell histologic activity index (HAI), and HBV genotype (C vs. non-C). Race was not considered simultaneously with genotype because 97% of patients harboring HBV genotype C were Asian, while <1% were Caucasian. Geographic location had a similar correlation with genotype, and therefore, these parameters were not considered simultaneously. A p value of <0.25 was required for model entry and <0.10 to stay.

3. Results

3.1. HBeAg-positive patients

3.1.1. Baseline characteristics associated with outcomes at 2 years

In the model including all baseline variables, serum HBV DNA levels <9 $\log_{10}$ copies/mL or ALT levels ⩾2.0 ×ULN were strong predictors for better virological outcomes at 2 years, including non-detectable serum HBV DNA ($p < 0.0001$ and 0.0002, respectively) and HBeAg seroconversion ($p = 0.004$ and <0.0001, respectively). Baseline HBV DNA level was also a significant predictor of low resistance at 2 years ($p < 0.0001$) – odds ratio [OR] with 95% CI for baseline HBV DNA <9 vs. ⩾9 $\log_{10}$ copies/mL is 0.28 (0.15, 0.53).

The baseline ALT levels (<2 ×ULN, 2–5 ×ULN, or >5 ×ULN) showed a positive correlation with the rates of HBV DNA negativity, HBeAg loss and HBeAg seroconversion at 2 years, while there was an inverse relationship with resistance (Table 2). Importantly, within each baseline ALT category, the rates of serum HBV DNA negativity at 2 years were higher with telbivudine, compared with lamivudine. Next, we compared the outcomes after 2 years of telbivudine treatment in all HBeAg-positive patients ($n = 458$) with the subgroup ($n = 80$) who had favourable baseline characteristics (ALT ⩾2×ULN and HBV DNA < 9 $\log_{10}$ copies/mL, Table 3). The latter subgroup demonstrated markedly better results at 2 years, compared with telbivudine recipients overall (Table 3).

Apart from HBV DNA and ALT levels at baseline, a lower BMI (<22.5 kg/m^2) was a significant predictor of non-detectable HBV DNA and ALT normalization at 2 years ($p = 0.0036$ and 0.0003 respectively), while younger age (<30 years) was a significant predictor of ALT normalization ($p = 0.0267$) and low resistance ($p = 0.0011$).

3.1.2. Early on-treatment responses correlate with outcomes at 2 years

The outcomes at 2 years for HBeAg-positive patients were significantly different for all outcome measures, depending on the HBV DNA levels at treatment week 12 or 24 (Table 4). These differences at 2 years were particularly marked for patients with non-detectable serum HBV DNA at week 12 or 24, compared with those in whom serum HBV DNA remained >4 $\log_{10}$ copies/mL. Importantly, the number of patients with non-detectable HBV DNA increased markedly between treatment week 12 to 24 (Fig. 1).

3.1.3. Correlation between combined baseline characteristics and on-treatment response with outcomes at 2 years

In addition to evaluating the predictive value of either baseline characteristics or early on-treatment responses

Table 2
Outcomes at 2 years based on serum ALT levels at baseline in HBeAg-positive patients.

HBeAg-positive outcomes at 2 years	ALT level at baseline					
	Lamivudine *n/N* (%)			Telbivudine *n/N* (%)		
	<2 ×ULN	2–5 ×ULN	>5 ×ULN	<2 ×ULN	2–5 ×ULN	>5 ×ULN
HBeAg seroconversion[a]	32/159 (20.0)	50/197 (25.4)	27/86 (31.2)	26/150 (17.8)	67/207 (32.3)	35/75 (46.3)
HBeAg loss[a]	39/159 (24.3)	59/197 (29.9)	31/86 (35.8)	36/150 (24.4)	79/207 (38.2)	37/75 (48.8)
Serum HBV DNA-negative	52/170 (30.4)	78/205 (37.7)	48/88 (54.3)	74/163 (45.7)*	125/219 (57.0)*	56/76 (73.3)*
Cumulative 1 log above nadir resistance (%)	78/170 (46.1)	83/205 (40.8)	22/88 (25.3)	47/163 (28.6)*	54/219 (24.5)*	14/76 (18.7)

[a] For HBeAg seroconversion and HBeAg loss, a patient needed to be HBeAg-positive at screening and at baseline to be included in this analysis which results in lower Ns as the other endpoints did not have this requirement.
* $p < 0.05$, telbivudine vs. lamivudine.

independently, we performed a multivariate analysis that combines the baseline variables and the magnitude of virologic response to telbivudine at treatment week 24 (Fig. 2). This demonstrated that non-detectable HBV DNA after 24 weeks treatment with telbivudine was the strongest predictor for serum HBV DNA negativity at 2 years (OR 5.87; $p < 0.001$), HBeAg seroconversion (OR 2.61 and $p < 0.001$), ALT normalization (OR 2.69; $p = 0.0002$) and for low telbivudine resistance (OR 0.16; $p < 0.0001$) in HBeAg-positive patients. Week 24 HBV DNA is significant even after adjusting for all baseline covariates (Fig. 2).

Serum HBV DNA negativity at weeks 12 and 24 were both introduced in the stepwise logistic regression model considering baseline and on-treatment factors. In HBeAg-positive patients, serum HBV DNA negativity at week 24 was a significant predictor (all $p < 0.0001$) for all endpoints, while serum HBV DNA negativity at week 12 was not significant ($p > 0.05$) or not selected.

3.1.4. Outcomes in HBeAg-positive patients with favourable baseline characteristics and early on-treatment response

We further examined the outcomes of treatment with telbivudine in the subgroup of patients with baseline HBV DNA $<9\log_{10}$ copies/mL and ALT $\geqslant 2$ ×ULN, and taking into account their early on-treatment response. The proportion of patients who achieved undetectable HBV DNA at week 24 was markedly higher in this subgroup than in all HBeAg-positive patients in the study – 71% vs. 45%, respectively. In addition, 52% of patients with undetectable HBV DNA at week 24 underwent HBeAg seroconversion (Fig. 3). Conversely, the rate of resistance at 2 years for these patients was markedly lower than in the overall HBeAg-positive population (1.8% vs. 25.1%).

3.2. HBeAg-negative patients

3.2.1. Baseline characteristics associated with outcomes at 2 years

Low BMI was the only significant predictor of non-detectable HBV DNA at 2 years ($p = 0.0107$), while age was the only significant predictor of serum ALT normalization ($p = 0.0174$). Baseline predictors of resistance at 2 years were baseline Knodell HAI (OR 5.16; $p = 0.0156$), baseline Ishak fibrosis score (OR 0.08; $p = 0.0002$), HBV genotype (OR 0.17; $p = 0.0099$) and BMI (OR 0.23; $p = 0.0217$). Baseline HBV DNA levels were not a significant predictor of outcomes in HBeAg-negative patients. There was a trend for higher rates of efficacy and lower resistance at 2 years for HBeAg-negative patients with baseline HBV DNA $< 7\log_{10}$ copies/mL, compared with HBeAg-negative patients overall (Table 3).

3.2.2. Early on-treatment responses correlate with outcomes at 2 years

The outcomes at 2 years for HBeAg-negative patients were significantly different depending on serum HBV

Table 3
Outcomes at 2 years with telbivudine treatment according to baseline serum HBV DNA levels.

Two years outcome parameter	All patients (%)		Patients with low baseline HBV DNA(%)	
	HBeAg-positive *n/N* (%)	HBeAg-negative *n/N* (%)	HBeAg-positive *n/N* (%)	HBeAg-negative *n/N* (%)
Serum HBV DNA-negative	255/458 (55.6)	182/222 (82.0)	62/80 (77.3)	81/91 (89.2)
HBeAg seroconversion	128/432 (29.6)	–	33/70 (47.1)	–
ALT normalization	306/440 (69.5)	158/203 (77.8)	60/80 (75.0)	60/73 (82.0)
Resistance rate	115/458 (25.1)	24/222 (10.8)	9/80 (11.3)	3/91 (3.1)

Overall population (baseline ALT 1.3–10 ×ULN and baseline HBV DNA $> 6\log_{10}$ copies/mL) vs. patients with low baseline viraemia levels (HBV DNA $<9\log_{10}$ copies/mL and baseline ALT $\geqslant 2$ ×ULN [HBeAg-positive patients, $n = 80$], or baseline HBV DNA $<7\log_{10}$ copies/mL [HBeAg-negative patients, $n = 91$]).

Table 4
Outcomes at 2 years with telbivudine treatment according to early on-treatment response at treatment week 12 or 24.

	Serum HBV DNA (copies/mL) Treatment week 12				Serum HBV DNA (copies/mL) Treatment week 24			
Week 104 outcome	<300	300–<3log$_{10}$	3– < 4log$_{10}$	>=4log$_{10}$	<300	300– <3log$_{10}$	3– <4log$_{10}$	>=4log$_{10}$
HBeAg-positive								
Non-detectable serum HBV DNA[*]	74/84 (88%)	44/55 (80%)	79/129 (61%)	58/183 (32%)	166/203 (82%)	35/57 (61%)	33/83 (40%)	21/107 (20%)
HBeAg seroconversion	33/72 (46%)	20/49 (41%)	46/125 (37%)	29/180 (16%)	84/183 (46%)	21/54 (39%)	17/81 (21%)	6/107 (6%)
Viral resistance[a]	5/84 (6%)	7/55 (13%)	30/129 (23%)	73/183 (40%)	18/203 (9%)	17/57 (30%)	34/83 (41%)	46/107 (43%)
HBeAg-negative								
Non-Detectable serum HBV DNA[*]	97/107 (91%)	39/47 (83%)	29/40 (73%)	16/27 (59%)	156/177 (88%)	14/18 (78%)	10/16 (63%)	2/10 (20%)
Viral resistance[a]	3/107 (3%)	5/47 (11%)	6/40 (15%)	10/27 (37%)	11/177 (6%)	4/18 (22%)	5/16 (31%)	7/10 (70%)

[a] Viral resistance is defined as viral breakthrough with treatment-emergent resistance mutations confirmed by genetic sequencing at week 104. In the study protocol, viral breakthrough was defined primarily as an increase of serum HBV DNA to at least 5log$_{10}$ copies/mL, following reduction to below that level. During the course of the study, this definition was superseded by the simpler and more widely accepted definition that pertains to the data reported above.

[*] These data together with Fig. 1 demonstrate the marked increase of the number of patients with non-detectable serum HBV DNA between week 12 and week 24, both in the HBeAg-positive and in the HBeAg-negative patients.

DNA levels at treatment weeks 12 or 24 (Table 4). Similar to the finding in HBeAg-positive patients, the proportion of HBeAg-negative patients with non-detectable HBV DNA increased markedly between treatment week 12 to 24 – from 48% to 80% (Fig. 1).

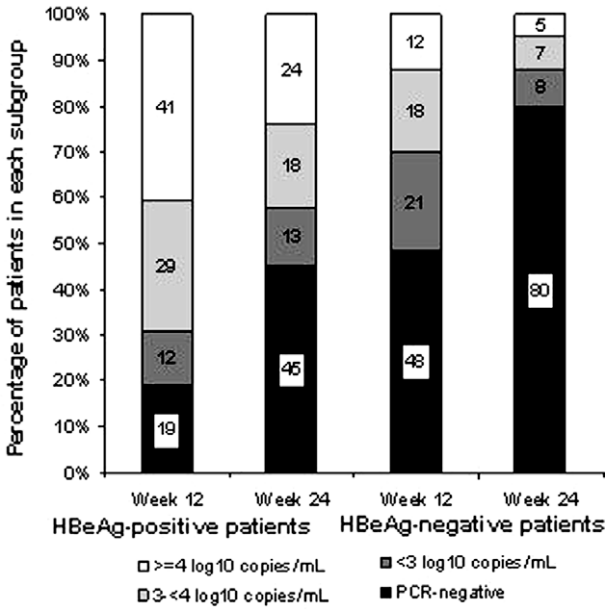

Fig. 1. Distribution of serum HBV DNA levels at treatment weeks 12 and 24. Data indicate the proportions of telbivudine recipients at each timepoint with serum HBV DNA levels: PCR-negative, detectable but <3log$_{10}$ copies/mL, from 3 to <4 or ⩾4log$_{10}$ copies/mL. *Note:* Seven and 8 HBeAg-positive patients had missing HBV DNA at weeks 12 and 24, respectively. One HBeAg-negative patient had missing HBV DNA at week 12 and 24. HBeAg, hepatitis B e antigen; PCR, polymerase chain reaction.

3.3. Correlation between combined baseline variables and on-treatment response with treatment outcomes at 2 years

Similar to the results in HBeAg-positive patients, the multivariate analysis that combined the baseline variables and the virologic response to telbivudine at week 24 identified non-detectable HBV DNA at treatment week 24 as a significant predictor of all outcomes at 2 years in HBeAg-negative patients (Fig. 4). Non-detectable HBV DNA after 24 weeks treatment with telbivudine was the strongest predictor for serum HBV DNA negativity at 2 years for HBeAg-negative patients (OR 9.76; $p < 0.0001$), ALT normalization (OR 3.98; $p = 0.0015$) and for low telbivudine resistance in (OR 0.06; $p < 0.0001$). Baseline variables such as BMI, age, Ishak fibrosis score or HBV genotype, that correlated significantly with 2-year outcomes, became weaker or non-significant when non-detectable HBV DNA at week 24 was included in the model (Fig. 4).

In the combined model, non-detectable serum HBV DNA at treatment week 12 was also a significant predictor of most 2-year outcomes, although the impact of serum HBV DNA negativity at week 12 was generally less than at week 24, with lower odds ratios and retention of all significant baseline variables that were identified in the initial model when using the baseline variables alone.

3.4. Outcomes in HBeAg-negative patients with favourable baseline characteristics and early on-treatment response

Amongst all HBeAg-negative patients, the subgroup with HBV DNA <7log$_{10}$ copies/mL at baseline and serum HBV DNA-negative at treatment week 24, 95% of telbivudine-treated patients achieved non-detectable

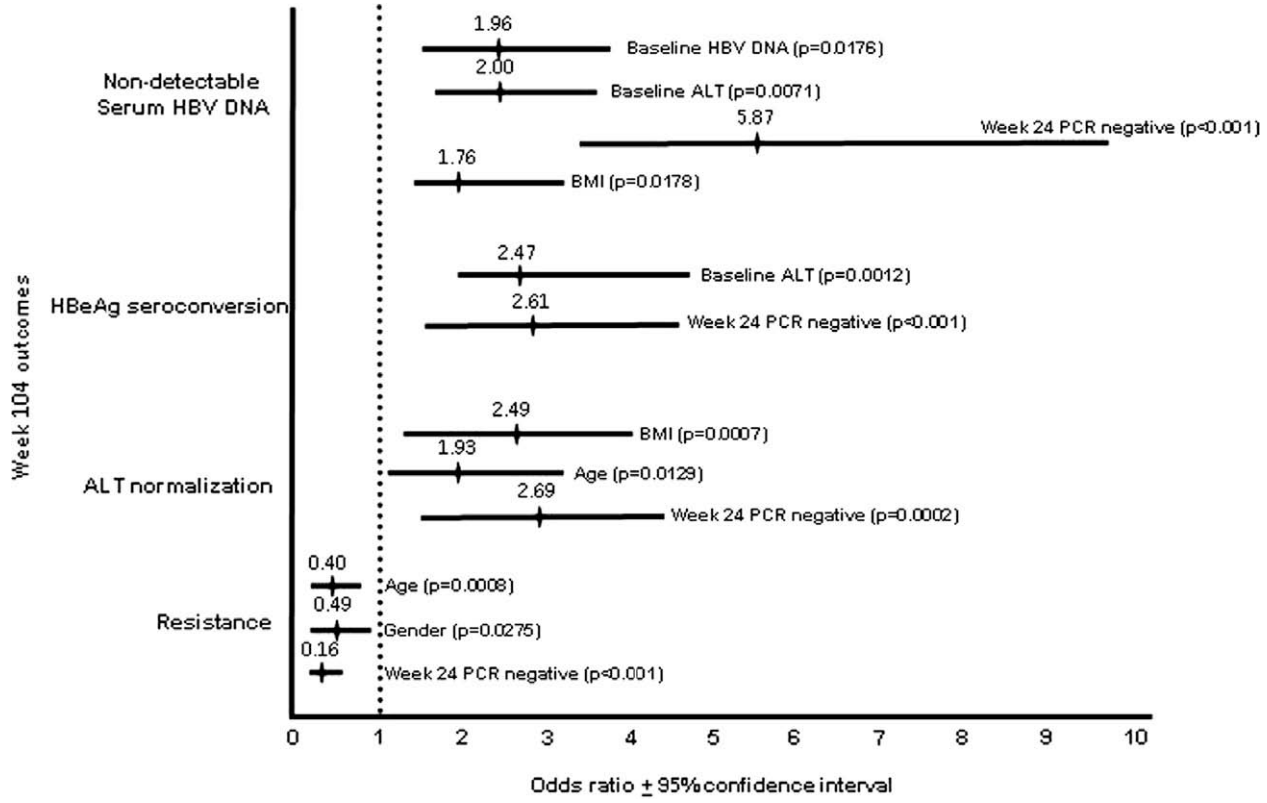

Fig. 2. Multivariate logistic regression analyses of baseline and on-treatment (week 24) predictors of week 104 outcomes in HBeAg positive patients. Predictors of 2-year treatment outcomes for HBeAg-positive telbivudine recipients. Combined baseline variables and the on-treatment response (non-detectable HBV DNA at week 24) are shown that were identified by multivariate analysis as significant predictors of outcomes after 2 years of telbivudine treatment. Data indicate odds ratios ± 95% confidence intervals. Odds ratios >1 indicate direct relationships; odds ratios <1 indicate inverse relationships. Selection criteria were: baseline HBV DNA <9 vs. $\geqslant 9 \log_{10}$ copies/mL; baseline ALT $\geqslant 2.0$ ×ULN vs. <2.0 ×ULN; baseline BMI <22.5 vs. $\geqslant 22.5$; Age <30 vs. $\geqslant 30$; baseline Ishak fibrosis score <3 vs. $\geqslant 3$; baseline Knodell HAI score $\leqslant 10$ vs. >10; HBV genotype C vs. non-C; gender female vs. male. ALT, alanine aminotransferase; BMI, body mass index; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; PCR, polymerase chain reaction.

HBV DNA vs. 82% in the overall HBeAg-negative population. In this subgroup, non-detectable HBV DNA at treatment week 24 was predictive of better outcomes with 91% of patients maintaining serum HBV DNA-negative at 2 years (Fig. 5). In addition, the rate of resistance at 2 years for this subgroup of HBeAg-negative patients was only 2.3% vs. 10.8% in the total HBeAg-negative population.

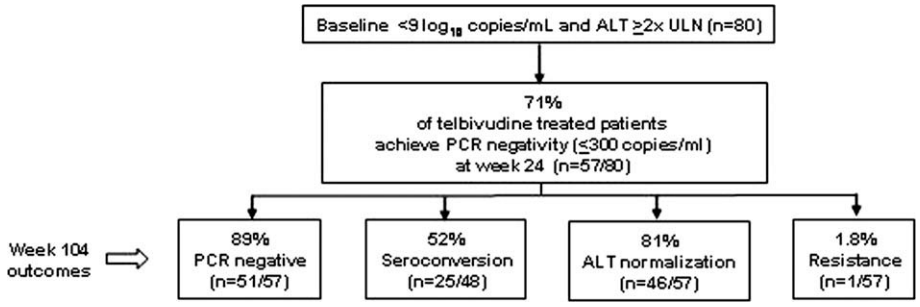

Fig. 3. Outcomes at 2 years for HBeAg-positive telbivudine recipients with favourable baseline characteristics and non-detectable serum HBV DNA at treatment week 24. Outcomes at 2 years are shown for patients who (1) were identified as optimal candidates for telbivudine therapy according to baseline disease characteristics (HBV DNA $<9 \log_{10}$ copies/mL and ALT $\geqslant 2$ ×ULN) and (2) achieved PCR-negative serum HBV DNA after 24 weeks of telbivudine therapy. Three patients withdrew before week 104 with no viral breakthrough or resistance. At week 104, 1 patient had low viral load ($2.5 \log_{10}$) without meeting the 1 log above nadir breakthrough definition, 1 patient had breakthrough with resistance and 1 patient had breakthrough with no resistance. ALT, alanine aminotransferase; HBeAg, hepatits B e antigen; HBV, hepatitis B virus; PCR, polymerase chain reaction; ×ULN, times the upper limit of normal.

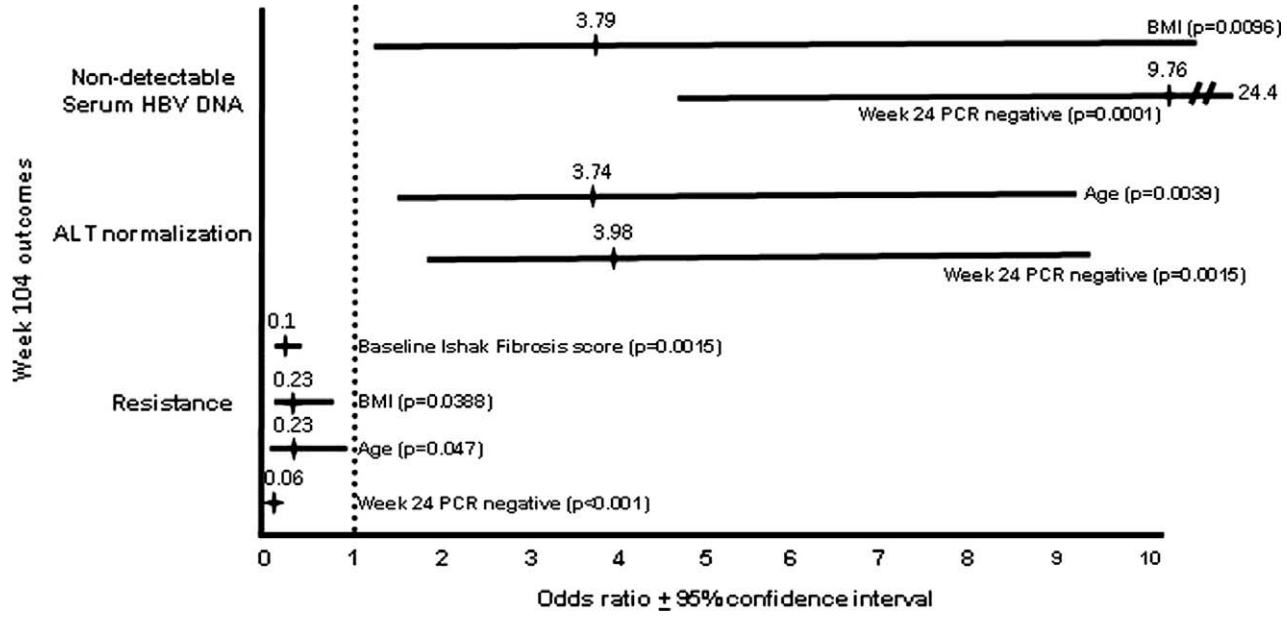

Fig. 4. Multivariate logistic regression analyses of baseline and on-treatment (week 24) predictors of week 104 outcomes in HBeAg negative patients. Significant predictors of 2-year outcomes for HBeAg-negative telbivudine recipients. Combined baseline variables and the on-treatment response (non-detectable HBV DNA at week 24) are shown that were identified by multivariate analysis as significant predictors of outcomes after 2 years of telbivudine treatment. Data indicate odds ratios ± 95% confidence intervals. Odds ratios >1 indicate direct relationships; odds ratios <1 indicate inverse relationships. Selection criteria were: baseline HBV DNA <7 vs. $\geqslant 7 \log_{10}$ copies/mL; baseline ALT $\geqslant 2.0 \times$ULN vs. <2.0 $\times$ULN; baseline BMI <24.5 vs. $\geqslant 24.5$; age <43 vs. $\geqslant 43$; baseline Ishak fibrosis score <3 vs. $\geqslant 3$; baseline Knodell HAI score $\leqslant 10$ vs. >10; HBV genotype C vs. non-C; gender female vs. male. ALT, alanine aminotransferase; BMI, body mass index; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; PCR, polymerase chain reaction.

4. Discussion

This study represents the most comprehensive and definitive analysis of pretreatment patients' characteristics and on-treatment responses, alone and in combination, as predictors of the treatment outcomes with an oral antiviral agent. The unique features of this investigation include the large cohorts of HBeAg-positive and HBeAg-negative patients and the intent-to-treat analyses of treatment outcomes after 2 years continuous telbivudine therapy. The robust results of these analyses are supported by the fact that all patients, who prematurely discontinued the study for various reasons, other than HBeAg seroconversion, were considered to have failed the endpoints. Pretreatment serum HBV DNA levels $<9 \log_{10}$ copies/mL and ALT levels $\geqslant 2 \times$ULN for HBeAg-positive patients, or pretreatment HBV DNA levels $<7 \log_{10}$ copies/mL for HBeAg-negative

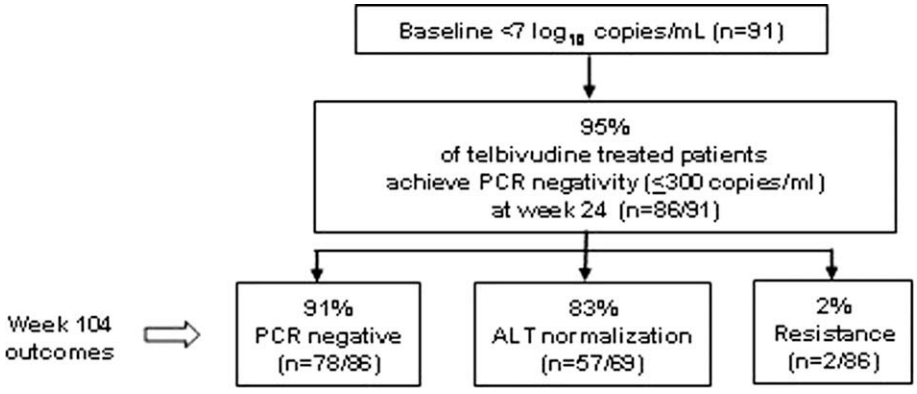

Fig. 5. Outcomes at 2 years for HBeAg-negative telbivudine recipients with favourable baseline characteristics and PCR-negative serum HBV DNA at week 24. Two-year outcomes are shown for patients who (1) were identified as optimal candidates for telbivudine therapy according to baseline disease characteristics (HBV DNA <7 $\log_{10}$ copies/mL) and (2) achieved PCR-negative serum HBV DNA after 24 weeks of telbivudine therapy. Three patients withdrew before week 104 with no viral breakthrough or resistance. At week 104, 2 patients had low viral load (<3 $\log_{10}$) without meeting the 1 log above nadir breakthrough definition, 2 patients had breakthrough with resistance and 1 patient had breakthrough with no resistance. ALT, alanine aminotransferase; HBeAg, hepatits B e antigen; HBV, hepatitis B virus; PCR, polymerase chain reaction; $\times$ULN, times the upper limit of normal.

patients, were associated with very high rates of nondetectable HBV DNA after 2 years of telbivudine treatment, as well as lower telbivudine resistance. Recent survey data indicate that patients with such pretreatment disease characteristics predominate in clinical practice [25,26]. However of all parameters analysed, serum HBV DNA level at treatment week 24 was the strongest predictor of 2 years efficacy outcomes with telbivudine.

HBeAg seroconversion has been established as a key marker for treatment success in HBeAg-positive chronic hepatitis B [4–7,12,13,24], as it is associated with improved long-term outcomes [2,3], and allows stopping treatment in patients with sustained control of HBV replication and disease remission. Similar to previous analyses for interferon or lamivudine treatment [8,9,13,14], the present study shows that increased serum ALT levels at baseline predict a higher rate of HBeAg seroconversion with telbivudine. Importantly, 32% of patients with pretreatment ALT levels between 2 and 5 $\times$ULN and 46% of those with ALT $>$ 5 $\times$ULN achieved HBeAg seroconversion after 2 years of treatment with telbivudine, which are generally similar or slightly greater than the corresponding rates of 30% and 41%, respectively, as a result of 1-year treatment with peg-interferon in patients with the same characteristics [24]. A recent study found that serial HBeAg quantitation is a useful indicator of seroconversion in patients treated with peg-interferon [27]. Given the similar rates achieved by one year treatment with peginterferon or with 2 years treatment with telbivudine, future studies will need to explore the predictive value of HBeAg quantitation during telbivudine therapy.

In HBeAg-negative patients baseline serum HBV DNA level was not a significant predictor of the 2-year outcomes for HBeAg-negative patients in the multivariate analysis; however, the high rate of serum HBV DNA negativity at week 24 in this group may have limited the ability of the statistical model to detect a significant relationship. HBeAg-negative patients with baseline serum HBV DNA less than 7 $\log_{10}$ copies/mL had more favourable outcomes at 2 years compared with the overall HBeAg-negative population, particularly for serum HBV DNA negativity and resistance, suggesting that baseline viral load may influence outcomes despite the results of the multivariate analysis.

Monitoring serum HBV DNA levels is a key component for assessment of on-treatment response and on treatment viral suppression correlates with improvement of liver histology [28]. In the present study, the multivariate analyses identified treatment week 24 as the optimal time point for evaluating the initial response to telbivudine based on serum HBV DNA levels which was predictive of the outcome after 2 years of treatment for both HBeAg-positive and HBeAg-negative telbivudine recipients. Treatment week 12 was found to be a premature time-point for decision on early treatment response and for predicting 2-year outcomes, as the proportion of patients with non-detectable serum HBV DNA markedly increased between weeks 12 and 24 of telbivudine treatment. The importance of maximal viral suppression at week 24 as a predictor of long-term results was first reported for lamivudine [16]. In addition, serum HBV DNA below 2000 copies/mL at treatment week 4 identifies a subset of patients with ideal 5-year response to lamivudine [29]. During adefovir treatment, HBV DNA greater than 1000 copies/mL at treatment week 48 was a significant predictor of high resistance to adefovir [30], while the HBV DNA level at treatment week 24 was a better predictor for adefovir response in lamivudine-resistant chronic hepatitis B [31]. The results of the GLOBE trial showed a clear difference in all outcomes after 2 years of treatment in patients who had non-detectable HBV DNA at week 24 compared to the group in whom HBV DNA was still detectable [22]. This data suggests that this would be an appropriate time to consider modification of therapy in the latter cases. Previous studies have also shown that high HBV DNA levels on-treatment is a marker of suboptimal response to interferon [14,15,29], as well as to oral antiviral agents [19,30,31]. Treatment modification aimed at further suppressing HBV DNA levels in these patients could be achieved by either adding another agent or switching to a different regimen. *De novo* combinations of two oral antiviral agents have failed to demonstrate greater antiviral activity than monotherapy [32,33]. One exception is the combination of a nucleoside analogue plus adefovir which was more potent than adefovir monotherapy [34]; however this is a reflection of the relatively weak antiviral effect of adefovir rather than the greater potency of the combination. In addition, *de novo* combination of lamivudine plus adefovir was not able to abolish the emergence of lamivudine resistance [33], while the addition of adefovir in patients with resistance to lamivudine or telbivudine was effective in suppressing the replication of drug-resistant HBV [22,35,36]. This data supports the add-on strategy, if needed, rather than *de novo* combination as a standard practice for all patients. *In vitro* data also suggest that the combination of telbivudine plus tenofovir has an additive antiviral effect with greater suppression of HBV replication than either drug alone [37]. Future clinical studies will need to evaluate whether the addition of tenofovir to telbivudine after 24 weeks of treatment in patients who are still HBV DNA-positive will further suppress HBV replication to a non-detectable level, or whether the benefit will only be to reduce the emergence of resistance during long-term treatment.

In conclusion, this study demonstrates that baseline characteristics and early on-treatment responses are useful in predicting the long-term outcomes of telbivudine treatment in both HBeAg-positive and HBeAg-negative

chronic hepatitis B. The assessment of early viral response by measurement of serum HBV DNA levels at treatment week 24 is the strongest predictor of all efficacy outcomes after 2 years of treatment with telbivudine.

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