

BASELINE CHARACTERISTICS AND EARLY VIROLOGIC RESPONSE TO TELBIVUDINE PREDICT 2-YEAR OUTCOMES FOR PATIENTS WITH HBEAG-NEGATIVE CHRONIC HEPATITIS B (THE GLOBE STUDY)

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Background

- The major treatment objective in chronic hepatitis B is to achieve sustained suppression of hepatitis B virus (HBV) replication, and long-term therapy is often required to maintain response.^{1,2}
- There are few data available to guide clinical decision-making regarding individual patient management and early evaluation of treatment response. The ability to predict long-term treatment response based on baseline demographics and early responses to therapy may help physicians individualize patient management and optimize outcomes in hepatitis B e-antigen (HBeAg)-negative chronic hepatitis B.
- The large phase III GLOBE study compared the efficacy and safety of telbivudine 600 mg/day and lamivudine 100 mg/day in 1367 adult patients (including 446 HBeAg-negative patients) with compensated chronic hepatitis B.³ Due to its size, the GLOBE study provides an excellent resource for assessing factors that may contribute to therapeutic outcomes.
- The aim of this analysis is to assess baseline characteristics and HBV DNA levels at Week 24 as predictors of outcomes among patients with HBeAg-negative chronic hepatitis B following 2 years of treatment with telbivudine, and to compare long-term outcomes achieved with telbivudine and lamivudine.

Methods

- The GLOBE study enrolled 1367 nucleos(t)ide-naïve patients aged 16–70 years, including 446 HBeAg-negative patients, with compensated CHB.
- Study endpoints assessed in this analysis include serum HBV DNA negativity (≤ 300 copies/mL), alanine aminotransferase (ALT) normalization, and resistance at Week 104 (2 years). Serum HBV DNA was quantified by COBAS[®] AmpliCor polymerase chain reaction (PCR) assay (detection limit 300 copies/mL). Resistance was defined as viral breakthrough (increase of serum HBV DNA ≥ 1 log above nadir) with confirmed genotypic resistance, based on the full length DNA sequencing of the reverse transcriptase domain of HBV polymerase.
- Multivariate regression analyses were used to identify and assess baseline and early on-treatment (Week 24) variables predictive of Week 104 efficacy outcomes. The population for these analyses comprised HBeAg-negative telbivudine recipients with available Week 104 data.
- Baseline variables included in the model were age, body mass index (BMI), serum ALT, Ishak fibrosis score, serum HBV DNA level, Knodell histologic activity index (HAI) score, gender, and HBV genotype. Continuous variables were dichotomized along the median of HBeAg-negative groups. *P*-values < 0.15 were required for model entry and > 0.25 for model exit.
- For analysis of on-treatment predictive factors, patients were categorized according to serum HBV DNA level at Week 24: PCR-negative; $< 3 \log_{10}$ copies/mL; $3-4 \log_{10}$ copies/mL; and $\geq 4 \log_{10}$ copies/mL.

Results

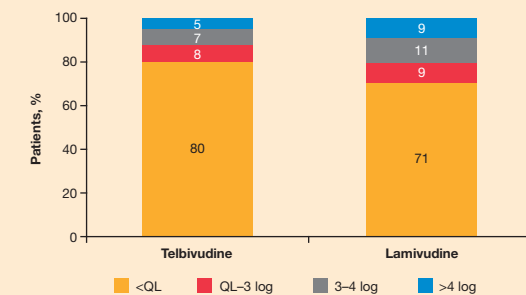
HBeAg-Negative Patient Population

- The intent-to-treat population of the GLOBE study comprised 446 HBeAg-negative patients treated with telbivudine ($n=222$) or lamivudine ($n=224$).

Outcomes in HBeAg-Negative Patients, Telbivudine vs. Lamivudine

- Telbivudine was associated with early, profound viral suppression by 24 weeks of treatment. A greater percentage of HBeAg-negative patients receiving telbivudine were serum HBV DNA PCR-negative, compared with lamivudine ($P<0.05$) (Figure 1).
- At Week 104, telbivudine demonstrated superiority on all direct measures of antiviral efficacy among HBeAg-negative patients (Table 1).

Figure 1. Viral load achieved by Week 24, telbivudine vs. lamivudine, HBeAg-negative patients.



QL, quantitation limit; PCR nondetectable at < 300 copies/mL by COBAS[®] AmpliCor. * $P<0.05$, telbivudine vs. lamivudine.

Table 1. GLOBE study results at 104 weeks among HBeAg-negative patients

	HBeAg-negative patients		
	Telbivudine	Lamivudine	<i>P</i>
N	222	224	—
Therapeutic response ¹ , %	78	66	0.007
Mean HBV DNA reduction from baseline, \log_{10} copies/mL	-5.0	-4.2	0.0002
HBV DNA PCR-negative, %	82	57	< 0.0001
ALT normalization, %	78	70	0.073
Resistance ² , %	11	26	< 0.0001

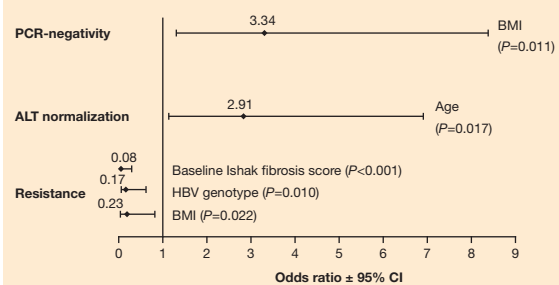
¹Serum HBV DNA $\leq 5 \log_{10}$ copies/mL coupled with ALT normalization.

²Viral breakthrough at Week 104 (persistent increase of HBV DNA of 1 log $>$ nadir value) with confirmed resistance mutations. Resistance rates at Week 104, calculated using protocol definition of viral breakthrough (persistent increase of HBV DNA to above 5 \log_{10} copies/mL after suppression to below that level), were 8% and 20% for telbivudine and lamivudine, respectively, in HBeAg-negative patients.

Baseline Variables Associated with Week 104 Outcomes, HBeAg-Negative Patients

- In HBeAg-negative telbivudine recipients, BMI was the only significant predictor of PCR-negativity at Week 104 ($P=0.011$), and age was the only significant predictor of ALT normalization ($P=0.017$) (Figure 2). BMI ($P=0.022$), Ishak fibrosis score < 3 ($P<0.001$), and genotype C ($P=0.010$) were predictors of Week 104 resistance.
- Because of a trend suggesting better Week 104 outcomes for HBeAg-negative patients with baseline HBV DNA $< 7 \log_{10}$ copies/mL, data from these patients were analyzed separately. A total of 194 HBeAg-negative patients with HBV DNA $< 7 \log_{10}$ copies/mL were randomized to telbivudine ($n=91$) or lamivudine ($n=103$). The groups were well-matched at baseline.
- Significantly more HBeAg-negative telbivudine recipients with baseline HBV DNA $< 7 \log_{10}$ copies/mL were HBV DNA PCR-negative at Week 24, compared with lamivudine (95% vs. 81%, $P=0.0039$) (Figure 3).
- At Weeks 52 and 104, telbivudine demonstrated higher rates of efficacy responses and less resistance among HBeAg-negative patients with HBV DNA $< 7 \log_{10}$ copies/mL, compared with lamivudine (Table 2).

Figure 2. Baseline variables associated with Week 104 outcomes in HBeAg-negative telbivudine recipients.



Baseline variables that were identified by multivariate analysis as significant predictors of outcomes at Week 104 are shown. Data indicate odds ratios \pm 95% confidence intervals (CIs). Odds ratios > 1 indicate direct relationships; odds ratios < 1 indicate inverse relationships. Selection criteria: serum HBV DNA at Week 24 PCR-negative (< 300 copies/mL) vs. not PCR-negative; baseline HBV DNA < 7 vs. $> 7 \log_{10}$ copies/mL; BMI < 22.5 vs. ≥ 22.5 ; Age < 30 vs. ≥ 30 ; gender female vs. male.

Figure 3. Week 24 PCR-negativity in HBeAg-negative patients with baseline HBV DNA $< 7 \log_{10}$ copies/mL.

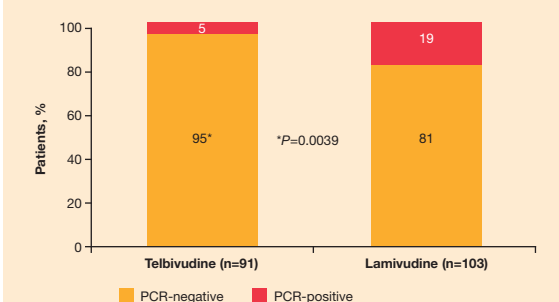


Table 2. GLOBE study results HBeAg-negative patients with baseline serum HBV DNA levels $< 7 \log_{10}$ copies/mL

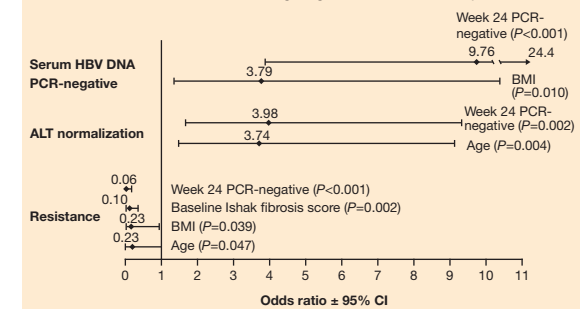
	HBeAg-negative patients with pretreatment serum HBV DNA levels $< 7 \log_{10}$ copies/mL					
	Week 52			Week 104		
	Telbivudine	Lamivudine	<i>P</i>	Telbivudine	Lamivudine	<i>P</i>
HBV DNA PCR-negative, n/N (%)	87/91 (96)	84/101 (83)	0.0094	81/91 (89)	69/101 (68)	0.0005
ALT normalization, n/N (%)	53/73 (73)	68/86 (79)	0.3407	60/73 (82)	69/86 (80)	0.7530
Resistance ¹ , n/N (%)	1/91 (1)	6/101 (6)	0.1217	3/91 (3)	21/101 (21)	0.0003

¹Viral breakthrough at Week 104 (persistent increase of HBV DNA of 1 log $>$ nadir value) with confirmed resistance mutations.

Early On-Treatment Variables Associated with Week 104 Outcomes, HBeAg-Negative Patients

- Viral load at Week 24 was the strongest predictor of Week 104 outcomes among HBeAg-negative patients. When Week 24 PCR-negativity was added to the multiple regression model, the predictive value of baseline parameters became weaker or insignificant, and Week 24 PCR-negativity remained the strongest predictor for PCR-negativity ($P<0.001$), ALT normalization ($P=0.002$), and resistance ($P<0.001$) at Week 104 (Figure 4).

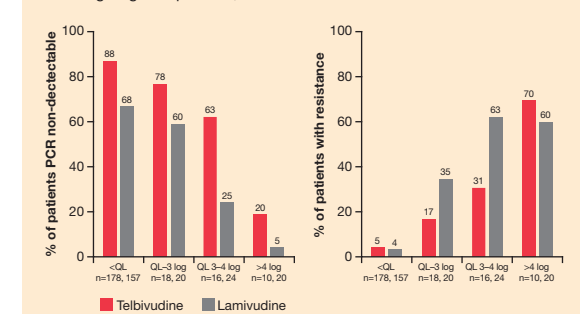
Figure 4. Significant baseline and on-treatment (Week 24) predictors of outcomes at Week 104 in HBeAg-negative telbivudine recipients.



Baseline and on-treatment variables that were identified by multivariate analysis as significant predictors of outcomes at Week 104 are shown, with PCR-negativity at Week 24 included in the statistical model. Data indicate odds ratios \pm 95% CIs. Odds ratios > 1 indicate direct relationships; odds ratios < 1 indicate inverse relationships. Selection criteria: serum HBV DNA at Week 24 PCR-negative (< 300 copies/mL) vs. not PCR-negative; baseline HBV DNA < 7 vs. $> 7 \log_{10}$ copies/mL; baseline ALT 32.5 x U/LN vs. < 2.5 x U/LN; BMI < 22.5 vs. ≥ 22.5 ; Age < 30 vs. ≥ 30 ; gender female vs. male.

- Patients who achieved PCR-negativity at Week 24 had higher rates of efficacy responses and less resistance at Week 104 in both treatment groups. Moreover, telbivudine demonstrated better outcomes than lamivudine at Week 104 within each Week 24 viral load subgroup (Figure 5).

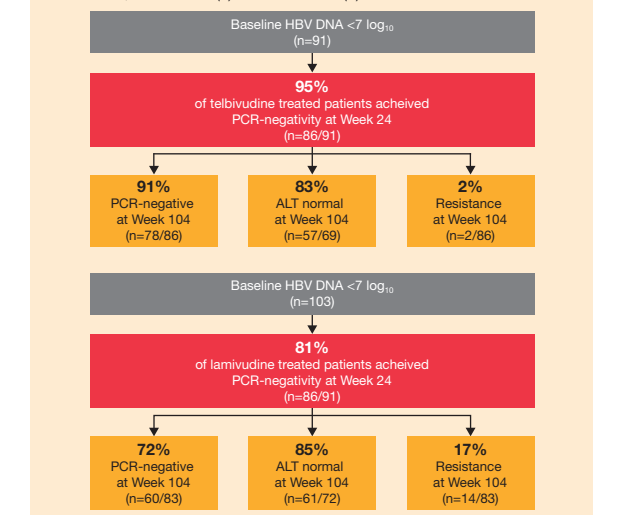
Figure 5. Effect of early (Week 24) viral response on Week 104 outcomes in HBeAg-negative patients, telbivudine vs. lamivudine.



¹Viral breakthrough at Weeks 52 and 104 (persistent increase of HBV DNA of 1 log $>$ nadir value) with confirmed resistance mutations.

- HBeAg-negative patients with baseline HBV DNA levels $< 7 \log_{10}$ copies/mL who were PCR-negative at Week 24 showed the highest rates of efficacy responses and the least resistance at Week 104. Predictability of long-term response was greater for telbivudine (91% PCR-negativity and 2% resistance at Week 104) than for lamivudine (72% PCR-negativity and 17% resistance at Week 104) (Figure 6).

Figure 6. Durability of outcomes at Week 104 among HBeAg-negative patients with baseline HBV DNA $< 7 \log_{10}$ copies/mL and PCR-negativity at Week 24, telbivudine (a) vs. lamivudine (b).



Conclusions

- In the GLOBE study, telbivudine demonstrated more profound early (Week 24) viral suppression and superiority on all direct measures of antiviral efficacy at Week 104 of treatment among HBeAg-negative patients, compared with lamivudine.
- Among HBeAg-negative patients with baseline HBV DNA level $< 7 \log_{10}$ copies/mL, telbivudine demonstrated higher rates of PCR-negativity at Week 24 and higher rates of efficacy responses and less resistance at Week 104, compared with lamivudine.
- Combining both baseline viremia and early on-treatment PCR-negativity at Week 24 can help identify HBeAg-negative chronic hepatitis B patients who can achieve optimal outcomes after 2 years of treatment.
- HBeAg-negative patients with baseline HBV DNA levels $< 7 \log_{10}$ copies/mL who were PCR-negative at Week 24 showed the highest rates of efficacy responses and the least resistance at Week 104 in both treatment arms, although predictability of long-term response was greater for telbivudine than for lamivudine.
- These results suggest that therapeutic outcomes may be optimized in HBeAg-negative patients through informed selection of initial therapy and by early evaluation of treatment response.

References

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