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CLINICAL STUDIES

Efficacy and safety of prolonged 3-year telbivudine treatment in patients with chronic hepatitis B

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Abstract

Background: In the GLOBE trial, telbivudine demonstrated superior efficacy to lamivudine at 2 years in patients with chronic hepatitis B (CHB). *Aims:* To investigate the long-term efficacy and safety of telbivudine in the telbivudine-treated cohort from the GLOBE trial. *Methods:* Virological and biochemical responses were assessed in 213 HBeAg-positive and 186 HBeAg-negative CHB patients who continued telbivudine treatment for 3 years. *Results:* Undetectable hepatitis B virus DNA and HBeAg seroconversions were achieved by 77 and 37% of HBeAg-positive patients respectively. Cumulative HBeAg seroconversion rate was 46%. HBeAg seroconversion was sustained at 52 weeks off therapy in 84% of the patients enrolled in the off-treatment follow-up arm of the study. Undetectable viraemia and normal alanine aminotransferase (ALT) levels at 3 years were achieved by 85 and 83% of HBeAg-negative patients respectively. Genotypic resistance rates for the study population who continued therapy during the third year were 11.3 in HBeAg-positive and 6.5% in HBeAg-negative patients. Patients with undetectable viraemia at treatment week 24 had optimal outcomes at 3 years. In the HBeAg-positive population, cumulative HBeAg seroconversion occurred in 58%. Resistance rates for HBeAg-positive and HBeAg-negative patients were 3.6 and 6.2% respectively. The telbivudine safety profile during prolonged therapy was similar to that in the GLOBE trial. *Conclusions:* Three years of telbivudine treatment yielded high rates of viral suppression and ALT normalization with a favourable safety profile. High rates of HBeAg seroconversion were achieved with prolonged telbivudine therapy and were sustained in the majority of patients over 52 weeks off therapy.

The management of patients with chronic hepatitis B (CHB) continues to evolve, with an expanded range of treatment options and an enhanced understanding of predictors of response to therapy. With the approval of entecavir, telbivudine and tenofovir, there are now five oral nucleos(t)ide analogs (NAs) available. Each of these new agents induces rapid and profound suppression of hepatitis B virus (HBV) replication, critical for attaining optimal treatment outcomes. On-treatment assessment of early virological response to oral NA therapy, as determined by undetectable serum HBV DNA at treatment week 24, is associated with better efficacy outcomes

at 1 year of treatment (1–8). Based on accumulating evidence, recent guidelines recommend monitoring on-treatment virological response at 24 weeks of NA therapy as a strategy for improving long-term treatment results (9–11). Clinical experience with oral NAs indicates that prolonged therapy (beyond 1 year) is necessary for most patients to achieve the primary goals of treatment, namely HBeAg seroconversion, alanine aminotransferase (ALT) normalization and sustained suppression of HBV replication below the level of detection using a polymerase chain reaction (PCR)-based assay (9–11). Limited information exists on the efficacy and predictors of response to oral NA treatment based on large cohorts of longitudinally followed patients with CHB beyond 2 years, particularly with the newer NAs.

The GLOBE trial, the largest intent-to-treat (ITT) analysis of prolonged NA treatment in patients with CHB conducted to date, demonstrated the superiority of telbivudine 600 mg/day over lamivudine 100 mg/day for all efficacy measures through 2 years of therapy (1, 12). A comprehensive analysis of pretreatment patient characteristics and on-treatment responses identified several baseline and early on-treatment characteristics that are useful in predicting the long-term outcomes of telbivudine treatment. Among all parameters in this analysis, serum HBV DNA level at treatment week 24 was the strongest predictor of efficacy outcomes after 2 years of telbivudine therapy in patients with HBeAg-positive and HBeAg-negative CHB (13).

The aims of the present study were to investigate the long-term safety and treatment efficacy of telbivudine in patients from the GLOBE trial who received continuous telbivudine therapy for 3 years, and to analyse the sustained off-treatment responses in patients who discontinued telbivudine therapy owing to efficacy. The relationship between early on-treatment virological response (PCR results at week 24) and treatment outcomes at 3 years with telbivudine was also examined.

Patients and methods

Study design and patients

In the GLOBE trial, the ITT population of telbivudine-treated patients included 458 HBeAg-positive and 222 HBeAg-negative patients ($N = 680$) who received 2 years of telbivudine therapy (12). At the end of treatment week 104, patients had the option to stop therapy, switch to another treatment or enroll in this open-label extension study in which all patients continued treatment with telbivudine 600 mg/day. At study entry, enrolled patients could have PCR-undetectable or PCR-detectable serum HBV DNA, but patients with demonstrated virological resistance at study entry were excluded from this analysis. Only patients treated with telbivudine in the GLOBE trial and enrolled in this extension study were considered for this analysis. All patients had the opportunity to roll over into study 2303, but 92 (24 HBeAg-negative and 68 HBeAg-positive) patients did not enroll at their own or the investigator's discretion. These patients were included in the 2-year ITT analysis of the GLOBE study; 32 were PCR negative, 60 were PCR positive and 41 had ALT normalization, with no additional data available.

A total of 484 patients from the GLOBE trial continued telbivudine treatment and enrolled in the present study (Fig. 1). Patients with protocol deviations during the third year of treatment ($n = 27$) were excluded from the efficacy analysis. Major reasons for protocol deviations included drug discontinuation because of treatment efficacy and noncompliance. The per-protocol population included 399 patients with CHB who met the above

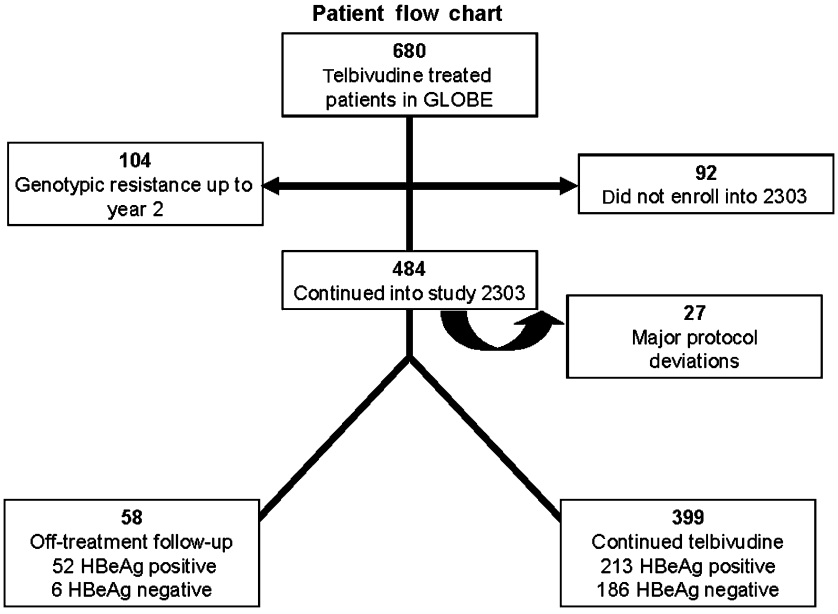

Fig. 1. Disposition for the patient population through week 156.

Table 1. Characteristics of patients enrolled in the GLOBE trial and study 2303

Characteristic	GLOBE Trial		Study 2303	
	HBeAg positive ($n = 458$)	HBeAg negative ($n = 222$)	HBeAg positive ($n = 213$)	HBeAg negative ($n = 186$)
Age, mean, years (range)	32 (16–63)	43 (17–68)	30 (16–59)	42 (17–68)
Male gender, *n* (%)	333 (73)	174 (78)	155 (73)	145 (78)
Weight, mean, kg (range)	66 (38–126)	72 (42–123)	64 (39–126)	70 (42–123)
Race, *n* (%)				
Asian	380 (83)	145 (65)	185 (87)	129 (69)
Caucasian	52 (11)	46 (21)	20 (9)	35 (19)
African, African American	4 (1)	3 (1)	0 (0)	3 (2)
Hispanic, Latino	2 (< 1)	2 (1)	0 (0)	1 (0.5)
Middle Eastern, Indian, Other	20 (4)	26 (12)	8 (4)	18 (10)
HBV genotype, *n* (%)				
A	24 (5)	12 (5)	6 (3)	7 (4)
B	129 (28)	59 (27)	63 (30)	48 (26)
C	259 (57)	89 (40)	123 (58)	84 (45)
D	42 (9)	57 (26)	20 (9)	43 (23)
Other, unknown	3 (1)	5 (2)	1 (0.5)	4 (2)
Serum HBV DNA, median, $\log_{10}$ copies/ml (range)	9.6 (3.8–16.0)	7.2 (3–13)	9.4 (3–16)	7.1 (3–13)
ALT, median, IU/l (range)	111 (19–1137)	99 (31–569)	112 (22–538)	98 (31–569)

ALT, alanine aminotransferase; HBV, hepatitis B virus.

criteria (213 HBeAg positive and 186 HBeAg negative). Of these patients, 46 (22%) of the 213 HBeAg-positive patients and seven (4%) of the 186 HBeAg-negative patients were HBV DNA positive at study entry. The patient population participating in the long-term extension study had baseline and disease characteristics similar to those of the original telbivudine-treated ITT cohort in the GLOBE trial (Table 1).

In addition, 52 telbivudine-treated HBeAg-positive patients who participated in the GLOBE trial and had discontinued treatment because of efficacy following protocol-specified criteria (i.e. who received ≥ 52 weeks of therapy had serum HBV DNA levels $< 5 \log_{10}$ copies/ml and demonstrated HBeAg loss for ≥ 24 weeks) before week 104 were enrolled in the off-treatment follow-up arm of the current study.

Efficacy assessment

Efficacy measures included the proportion of patients with undetectable serum HBV DNA (< 300 copies/ml) by PCR assay, normalization of ALT levels [$\leq 1 \times$ the upper limit of normal (ULN)], HBeAg loss, HBeAg seroconversion, HBsAg loss, HBsAg seroconversion and genotypic resistance at 3 years. As per the protocol, only those patients who had confirmed efficacy measures on two consecutive visits, without any intervening disqualifying values, were considered to have achieved an efficacy response. Subanalyses of efficacy outcomes at 3 years based on early virological response (undetectable HBV DNA at week 24) and maintained virological response (undetectable HBV DNA at on-treatment visits at weeks 24, 52, 76, 104 and 128) were also performed.

Off-treatment efficacy analyses included determination of the proportion of patients who sustained HBeAg loss and HBeAg seroconversion (the event was reported at two consecutive visits before study drug discontinuation and sustained off-treatment) at week 52 after stopping therapy with telbivudine. The off-treatment durability of HBeAg seroconversion for those patients with assessments available at week 52 is reported here.

Standardized tests were performed centrally by Quintiles Transnational (Research Triangle Park, Durham, NC, USA). Serum HBV DNA levels were quantified by the COBAS® Amplicor HBV Monitor PCR assay (Roche Molecular Systems, Pleasanton, CA, USA), which has a detection limit of 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.

Viral breakthrough and resistance analysis

Viral breakthrough was defined as a confirmed (by two consecutive determinations) increase in serum HBV DNA levels $> 1 \log_{10}$ copies/ml above nadir (14). As reported previously, resistance was defined as the emergence of treatment-associated resistance mutations, identified by direct sequencing of the HBV polymerase gene at week 156 in all patients with serum HBV DNA levels > 1000 copies/ml and compared with the HBV DNA sequences at baseline (12). Resistance rates were reported based on all per-protocol patients (213 HBeAg positive and 186 HBeAg negative). Serum HBV DNA was quantified by the COBAS® Amplicor HBV Monitor PCR assay (Roche Molecular Systems), which has a detection limit of 300 copies/ml. DNA sequencing was performed at an independent laboratory (Delft Diagnostic Laboratory, AD Delft, the Netherlands).

Safety assessment

The safety population consisted of 224 HBeAg-positive and 190 HBeAg-negative patients ($N = 414$). Adverse events (AEs) and laboratory abnormalities were monitored throughout the treatment phase and graded for severity according to the criteria adapted from the Division of Acquired Immunodeficiency Syndrome, National Institute of Allergy and Infectious Disease (15). ALT flares were defined as ALT elevations $> 2 \times$ baseline and > 10 ULN, as per the American Association for the Study of Liver Diseases (AASLD) practice guidelines (11). Grade 3/4 creatine kinase (CK) elevations were defined as CK levels $> 7 \times$ ULN.

Statistical analysis

As the 3-year analysis is intended to summarize efficacy and safety in patients continuously treated with telbivudine monotherapy only, no statistical comparison between treatment groups was performed. Analyses of 3-year efficacy results (HBV DNA < 300 copies/ml, ALT normalization, HBeAg and HBsAg loss and seroconversion) were based on all data observed, and missing data were not imputed. The cumulative HBeAg seroconversion rate was defined as the percentage of HBeAg-positive patients ($n = 213$) with documented seroconversion at any point during the 3-year treatment period, including patients who subsequently seroreverted. Analysis of off-treatment durability of efficacy responses included all HBeAg-positive patients in the GLOBE trial who discontinued treatment because of efficacy and were enrolled in the separate off-treatment follow-up portion of the current study. Prespecified analyses were undertaken to assess the relationships between early antiviral responses and efficacy outcomes at 3 years and included the proportions of patients with undetectable serum HBV DNA by PCR, HBeAg loss, HBeAg seroconversion, normal ALT levels and genotypic resistance. Patients were categorized at treatment week 24 as having PCR-undetectable or PCR-detectable HBV DNA. The chi-square test was used to assess the significance of the difference across the subgroups.

Results

Virological and biochemical responses at 3 years

Continued telbivudine treatment was associated with high rates of viral suppression and biochemical response in HBeAg-positive and HBeAg-negative patients (Table 2). At 3 years, 76.6% of HBeAg-positive patients had undetectable serum HBV DNA and 37.1% achieved HBeAg seroconversion. Most notably, the rate of cumulative HBeAg seroconversion increased with continued telbivudine treatment from 24.4% (52 of 213 patients) at week 52 to 37.6% (80 of 213 patients) at week 104 and 45.5% (97 of 213 patients) at week 156. HBsAg loss was documented in three patients (1.6%) with HBV genotypes C ($n = 2$) and D ($n = 1$). Of these, HBsAg

Table 2. Efficacy results at week 156 of telbivudine treatment*

	All per-protocol patients†		Patients with HBV DNA levels < 300 copies/ml at week 24		Patients with HBV DNA levels ≥ 300 copies/ml at week 24	
Characteristic	HBeAg positive ($n = 213$)	HBeAg negative ($n = 186$)	HBeAg positive ($n = 111$)	HBeAg negative ($n = 161$)	HBeAg positive ($n = 102$)	HBeAg negative ($n = 25$)
HBV DNA level < 300 copies/ml, *n* (%)	147/192 (76.6)	142/167 (85.0)	92/103 (89.3)‡	128/147 (87.1)§	55/89 (61.8)	14/20 (70.0)
ALT normalization, *n* (%)	149/184 (81)	125/151 (82.8)	81/98 (82.7)	111/132 (84.1)	68/86 (79.1)	14/19 (73.7)
HBeAg loss, *n* (%)	96/185 (51.9)	NA	65/98 (66.3)‡	NA	31/87 (35.6)	NA
HBeAg seroconversion, *n* (%)	69/186 (37.1)	NA	45/99 (45.5)§	NA	24/87 (27.6)	NA
HBsAg loss, *n* (%)	3/192 (1.6)	0/167 (0)	1/103 (1.0)	0/147 (0)	2/89 (2.2)	0/20 (0)
HBsAg seroconversion, *n* (%)	1/192 (0.5)	0/167 (0)	0/103 (0)	0/147 (0)	1/89 (1.1)	0/20 (0)
Resistance, *n* (%)	24/213 (11.3)	12/186 (6.5)	4/111 (3.6)	10/161 (6.2)	20/102 (19.6)	2/25 (8.0)

The denominator for each parameter reflects the number of patients available for assessment at the respective timepoint.

*As per the protocol, only those patients who had maintained efficacy measures on two consecutive visits and at last treatment visit, without any intervening disqualifying values, were considered to have achieved efficacy response.

†The overall population had no genotypic resistance at week 104 and were PCR positive or negative at enrollment into the study.

‡ < 0.0001 (the *P* values for the differences among the week 24 on treatment HBV DNA subgroups are based on a chi-square test).

§$P < 0.05$.

ALT, alanine aminotransferase; NA, not available; PCR, polymerase chain reaction.

seroconversion occurred in one patient with genotype C by week 156. In the group of HBeAg-negative patients, 85.0 had undetectable serum HBV DNA and 82.8% had normalized ALT at week 156 (Table 2).

Correlation of early on-treatment parameters with outcomes at 3 years

Early viral suppression by week 24 was associated with better outcomes at 3 years (Table 2). HBeAg-positive patients with undetectable viraemia by treatment week 24 achieved significantly higher rates of PCR-negative serum HBV DNA (89.3 vs 61.8%; $P < 0.0001$) and HBeAg seroconversion (45.5 vs 27.6%; $P = 0.0121$) at week 156 as compared with patients who had detectable viraemia at treatment week 24. The cumulative rate of HBeAg seroconversion increased to 57.7% by week 156 in patients with undetectable serum HBV DNA at treatment week 24 (Fig. 2). HBeAg-negative patients with undetectable viraemia by treatment week 24 also had significantly higher rates of PCR negativity than those with detectable viraemia at week 24 (87.1 vs 70.0%; $P = 0.0453$) (Table 2).

Maintained virological responses to telbivudine at 3 years

Currently, international treatment guidelines (9–11, 16) recommend that patients with early virological response (PCR negative at week 24) should be monitored every 6 months to confirm maintenance of viral suppression, to detect viral breakthrough and to decide on possible treatment modification. Analysis of patients with undetectable HBV DNA at treatment week 24 found 87 of HBeAg-positive patients (97 of 111) and 88% of HBeAg-negative patients (142 of 161) had maintained virological response at each 6-monthly visit during the 3 years of continuous telbivudine treatment (i.e. they were PCR negative at treatment weeks 24, 52, 76, 104 and 128). In this group of patients, 93 of HBeAg-positive and 94% of HBeAg-negative patients remained PCR negative at 3 years (Fig. 3).

Post-treatment durability of HBeAg seroconversion

In the GLOBE trial, 119 HBeAg-positive patients met the criteria for treatment discontinuation (HBeAg loss and HBV DNA levels $< 5 \log_{10}$ copies/ml with at least 6 months of consolidation treatment) and 52 of these stopped telbivudine treatment as per investigators' discretion. At treatment cessation, the majority of patients had HBeAg seroconversion (45 of 52 patients) and undetectable HBV DNA (50 of 52 patients). Of the 52 patients who discontinued telbivudine treatment because of efficacy, 38 (73%) were available for assessment at week 52 of off-treatment follow-up. HBeAg loss and seroconversion were durable in the majority of patients (Table 3), being sustained in 87 and 84% of patients respectively. At week 52 of off-treatment follow-up, 92% of patients with durable HBeAg seroconversion had serum HBV DNA levels $< 5 \log_{10}$ copies/ml, 77% had HBV DNA levels $< 4 \log_{10}$ copies/ml and 27% were PCR negative.

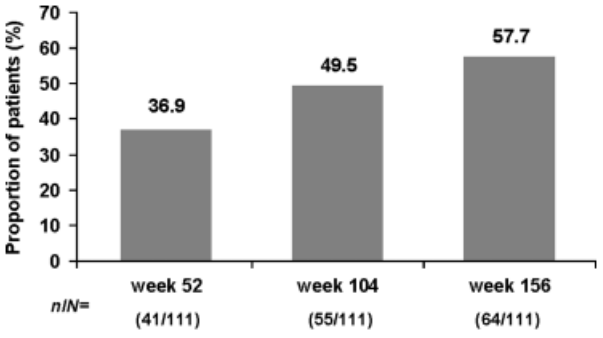

Fig. 2. Cumulative HBeAg seroconversion rates with continuous telbivudine treatment in per-protocol HBeAg-positive patients who had serum HBV DNA < 300 copies/mL by week 24. HBV, hepatitis B virus.

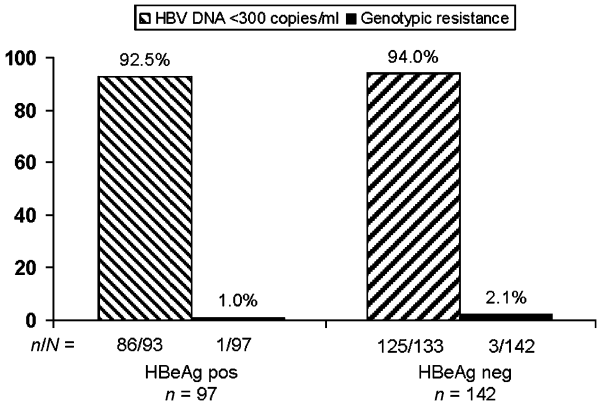

Fig. 3. Proportion of those patients with undetectable hepatitis B virus (HBV) DNA from weeks 24 through weeks 126, who have sustained PCR nondetectability at the end of 3 years continuous telbivudine and the proportion who have genotypic resistance.

Table 3. Durability of HBeAg loss and seroconversion at week 52 off treatment in patients who experienced HBeAg loss/seroconversion at the end of telbivudine treatment*

Sustained efficacy parameter	*n/N* (%)
Sustained HBeAg loss	33/38 (86.8)
Sustained HBeAg seroconversion	26/31 (83.9)
HBV DNA level $< 5 \log_{10}$ copies/ml	24/26 (92.3)†
HBV DNA level $< 4 \log_{10}$ copies/ml	20/26 (76.9)
HBV DNA level < 300 copies/ml	7/26 (26.7)†

*Only patients available for analysis at week 52 were reported.

†The 26 patients who sustained HBeAg seroconversion at week 52 off treatment.

HBV, hepatitis B virus.

Resistance

In per-protocol patients who could have undetectable or detectable PCR at study entry, genotypic resistance at week 156 was present in 11.3% of HBeAg-positive

patients and 6.5% of HBeAg-negative patients (Table 2). Undetectable viraemia at treatment week 24 of the GLOBE trial was associated with lower rates of genotypic resistance to telbivudine at week 156 in HBeAg-positive and HBeAg-negative patients (Table 2). Among patients with maintained virological response, resistance rates were low – 1.0% in HBeAg-positive patients and 2.1% in HBeAg-negative patients (Fig. 3).

Safety and tolerability

The safety profile of telbivudine over 3 years was similar to that reported at 2 years in the GLOBE trial; most AEs were mild and transient in nature and no new safety signals were observed. AEs over 3 years, which were possibly related to the study drug, were reported in 120 patients (29.0%). AEs leading to treatment cessation occurred in two (0.5%) patients. The most common treatment-related AEs were elevated CK levels (7.5%), headache (3.6%), fatigue (2.9%), nausea (2.9%), diarrhoea (2.2%) and nasopharyngitis (1.9%). Myalgia, myositis and muscular weakness were reported in 22 (5.3%), two (0.5%) and two (0.5%) patients respectively. Of these, only five cases of myalgia were considered possibly related to study treatment. Symptoms of paraesthesia ($n = 3$; 0.7%), neuralgia ($n = 1$; 0.2%), polyneuropathy ($n = 1$; 0.2%) and sensory loss ($n = 1$; 0.2%) were reported in six patients; however, only one patient (0.2%) had paraesthesia that was considered to be related to study treatment. A total of 55 patients (13.3%) developed new-onset grade 3/4 CK elevations ($> 7 \times$ ULN) by week 156 of telbivudine treatment; however, this did not correlate with musculoskeletal AEs and occurred sporadically throughout the 3 years. The majority (95.0%) of on-treatment grade 3/4 CK elevations were transient and resolved or decreased in grade by the time of the next CK determination. Serum ALT flares, as defined by the AASLD guidelines, occurred in 11 patients. One patient reported a serious AE, which was considered to be possibly related to the study drug (0.2%; nausea and dizziness). No peripheral neuropathy was reported.

During the 3 years of telbivudine therapy, serious AEs were reported in 28 patients (6.8% total). The most frequently reported SAEs were hepatocellular carcinoma, pneumonia and nephrolithiasis, each diagnosed in two patients (Table 4).

Table 4. Serious adverse events

	Number (%)
Serious adverse events	28 (6.8)
Hepatocellular carcinoma	2 (0.5)
Pneumonia	2 (0.5)
Nephrolithiasis	2 (0.5)
Fracture	1 (0.2)
Lymphoma	1 (0.2)
Depression	1 (0.2)
Pericarditis	1 (0.2)
Coronary artery disease	1 (0.2)
Retinal detachment	1 (0.2)
Nausea	1 (0.2)
Vomiting	1 (0.2)
Diabetic ketoacidosis	1 (0.2)
Hypoglycaemia	1 (0.2)

Discussion

Natural history and clinical cohort studies of CHB demonstrate that the sustained suppression of HBV DNA to very low levels and HBeAg seroconversion in HBeAg-positive patients are important end points of treatment and correlate with a reduction in disease progression (17, 18). Oral therapy with new and more potent NAs effectively induces rapid and profound suppression of HBV; however, long-term therapy with these agents is required to achieve the desired clinical outcomes (19). To date, the efficacy and safety of continuous prolonged therapy with newer oral NAs have been studied in only a small number of HBeAg-positive and HBeAg-negative patients (20–23). Interpretation of data from several of these long-term follow-up studies is limited by study designs, treatment gaps, the use of combination therapy and small patient populations (20, 22). The present study presents an analysis of the long-term safety, efficacy and off-treatment durability of HBeAg seroconversion response to telbivudine in a large cohort of continuously treated patients with HBeAg-positive and HBeAg-negative CHB.

In the GLOBE trial, telbivudine demonstrated superior 2-year efficacy to lamivudine in all direct measures of antiviral efficacy, with a favourable safety and tolerability profile (12). In the present investigation, 3 years of continuous telbivudine treatment was well tolerated and associated with a high rate of maintained virological and biochemical control in the patients studied. These findings further substantiate the efficacy of prolonged treatment with telbivudine for patients with CHB. Additionally, undetectable viraemia at week 24 continued to be an important predictor for favourable outcomes at 3 years.

In patients with HBeAg-negative CHB, profound and sustained suppression of HBV replication is the primary goal of treatment, and long-term NA treatment is necessary to maintain virological response in these patients (24, 25). Prolonged treatment for up to 2 years with entecavir and tenofovir is associated with high rates of sustained virological response (26, 27). In the phase III registration study ETV-027, only 8% of the HBeAg-negative entecavir-treated patients (26 of 325 patients) was continued on blinded treatment beyond 48 weeks. Of these 26 patients, 22 (84.6%) had undetectable viral load but only seven (26.9%) experienced ALT normalization at 96 weeks (27). In patients with HBeAg-negative CHB who received 96 weeks of continuous treatment with tenofovir in the phase III registration study 102, 91% (228 of 250 patients) achieved serum HBV DNA levels

< 400 copies/ml (26). In the 104-week ITT analysis of the GLOBE trial, 82% (182 of 222) of telbivudine-treated HBeAg-negative patients achieved undetectable viral load with higher rates of response seen in patients who were PCR negative at week 24 (12, 13). The majority (88%; 142 of 161) of HBeAg-negative patients who were PCR negative at week 24 maintained undetectable viraemia at each 6-month follow-up visit during the 3 years. Of these patients who had undetectable HBV DNA at week 24 of the GLOBE study and were monitored according to the 'roadmap concept' every 6 months, 94% maintained PCR negativity at 3 years. These findings demonstrate that telbivudine is a very effective and durable long-term treatment option for patients with HBeAg-negative CHB.

In patients with HBeAg-positive CHB, profound suppression of HBV replication and HBeAg seroconversion has been established as key markers of treatment success (28–32). Furthermore, HBeAg seroconversion provides patients with the possibility of stopping treatment, an option that had been considered previously primarily for treatment with the interferons (9–11, 33). Entecavir and tenofovir induce HBeAg seroconversion in 20 and 21% of patients, respectively, after 1 year of therapy (1, 34, 35). In the 96-week efficacy analysis of entecavir in patients with HBeAg-positive CHB, the cumulative rate of HBeAg seroconversion was 31% (110 of 354 patients) (20); however, lower rates of HBeAg seroconversion (21–24%) have been reported at 96 weeks in long-term follow-up studies of entecavir in Asian patients (36–38). In the tenofovir registration trial, an HBeAg seroconversion rate of 26% was reported at 96 weeks (22). In the 104-week ITT analysis of the GLOBE trial, continuous telbivudine treatment was associated with an HBeAg seroconversion rate of 30% (12). Data from the current study suggest that 3 years of telbivudine treatment is associated with continued clinical benefit, as indicated by increasing rates of HBeAg loss and seroconversion, leading to a cumulative HBeAg seroconversion rate of 46% in the long-term treatment group. Most notably, an even higher cumulative HBeAg seroconversion rate (58%) was achieved in patients who had undetectable viraemia at week 24. The exact mechanism for the enhanced HBeAg seroconversion rates observed with telbivudine treatment remains undefined, but preliminary evidence suggests that telbivudine may exert an immunological effect in addition to the suppression of viral replication (39, 40).

Current treatment guidelines indicate that patients should be considered for treatment when HBV DNA levels are above 10^4 copies/ml. HBeAg seroconversion with HBV DNA suppression after a finite period of oral NA therapy is an appropriate end point in most HBeAg-positive patients as long as appropriate monitoring is provided to detect for hepatitis reactivation (9–11). In the current study, HBeAg seroconversion induced with telbivudine was durable in the majority of patients for 1 year off treatment. Longer term follow-up data are currently being analysed. A high proportion of patients (77%) with durable off-treatment HBeAg seroconversion at week 52 had serum HBV DNA levels $< 4 \log_{10}$ copies/ml, allowing them to remain off treatment as long as continued monitoring was ensured.

The importance of monitoring early virological response and on-treatment serum HBV DNA levels has been proposed by Keeffe *et al.* (16) and has been incorporated into the latest expert guidelines for the management of CHB (9–11). Early on-treatment suppression of HBV DNA levels (24 weeks) with telbivudine was shown to be predictive of 2-year efficacy, and resistance with telbivudine (12, 13) continued to be an important predictor of favourable outcomes at 3 years.

The potential risk for the emergence of antiviral resistance and long-term safety remain a key issue for all chronic antiviral treatments. Clinical and virological studies have demonstrated the benefit of early treatment adjustment as soon as viral load increases (41). In the current analysis, telbivudine-treated patients who were monitored at each 6-monthly visit according to the recommended clinical practice, and who achieved undetectable HBV DNA at week 24 and remained PCR negative at each 6-monthly visit, experienced low levels of resistance (1% HBeAg positive and 2% HBeAg negative) at 3 years. In the entecavir long-term follow-up trial, low rates of resistance were reported (1.2% at 5 years). However, in this entecavir cohort, resistance rates were an estimation of the cumulative probability of resistance calculated for a small selected subgroup of virological responders of the original ITT population, who comprised the long-term efficacy cohort (42). Additionally, patients enrolled in the long-term follow-up analysis received a higher dose of entecavir (1 mg/day), which may have altered the risk of resistance in this population. Although no resistance was reported at 2 years of tenofovir treatment, the use of the block study design and addition of emtricitabine to tenofovir in patients who demonstrated a suboptimal response (i.e. serum HBV DNA levels $\geq$ 400 copies/ml) at week 72 may have masked the risk for resistance (22, 26). The results presented in this report confirm that implementing the 'roadmap concept' during telbivudine treatment with regular monitoring of HBV DNA levels every 6 months leads to low levels of resistance and may offer a high probability of HBeAg seroconversion. For patients with confirmed detectable viraemia at week 24 or further time points, intensification of treatment is recommended to enhance HBV suppression.

Continuous telbivudine treatment for up to 3 years was well tolerated in HBeAg-positive and HBeAg-negative patients with CHB. Grade 3/4 serum CK elevations were transient and generally resolved by the next follow-up visit. Persistent grade 3/4 CK elevations were not correlated with myositis, which occurred rarely. No new safety signals were observed during the third year of treatment, and the safety profile of telbivudine remains similar to that described in the 2-year GLOBE trial.

Conclusion

The current analysis evaluating continuous treatment with telbivudine over 3 years has shown that telbivudine therapy results in high virological and serological success with low levels of resistance in well-monitored patients with CHB with a favourable safety profile. Additional follow-up of these patients will provide more data on the durability of efficacy end points and further evidence for clinical improvement.

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