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ORIGINAL ARTICLE

Efficacy and resistance to telbivudine treatment in chronic hepatitis B patients with favorable predictors: a multicenter study in Taiwan

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Abstract

Background/purpose A subgroup analysis of a GLOBE study identified subgroups of chronic hepatitis B (CHB) patients with excellent outcomes to telbivudine (LdT) treatment. The aim of this study was to validate this concept using a real-world clinical population.

Methods This prospective, retrospective, and multicenter study examined both HBeAg-positive and HBeAg-negative CHB patients treated with LdT for 2 years.

Results A total of 116 CHB patients were recruited. Of the 64 HBeAg-positive patients, 35 had favorable baseline characteristics [hepatitis B virus (HBV) DNA ≤ 9 $\log^{10}$ copies/mL and alanine aminotransferase $\geq 2\times$ the upper limit of normal (ULN)], but only 40 % (14/35) achieved polymerase chain reaction (PCR) negativity at week 24. Among the 14 patients with favorable baseline characteristics and on-treatment response, the rates of virologic, biochemical, and serologic response and genotypic

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resistance were 78.6 % (11/14), 64.3 % (9/14), 50 % (7/14), and 7.1 % (1/14), respectively, at week 104 of therapy. Of the 52 HBeAg-negative patients, 34 met the criteria of a baseline serum HBV-DNA level less than 7 $\log^{10}$ copies/mL, and 29 (85.3 %) achieved PCR negativity at week 24. Among the 29 patients with favorable baseline characteristics and on-treatment response, the rates of virologic and biochemical response and genotypic resistance were 96.6 % (28/29), 72.4 % (21/29), and 6.9 % (2/29), respectively. In addition, the PCR negativity at week 24 was the only factor associated with the virologic response and genotypic resistance to LdT treatment.

Conclusion The efficacy and resistance to LdT treatment in CHB patients with favorable predictors were comparable between a real-world clinical population and the GLOBE study. In addition, PCR negativity at week 24 could predict virologic response and genotypic resistance to LdT treatment.

Keywords Hepatitis B virus · Telbivudine · Super-responder · Roadmap concept

Introduction

Hepatitis B virus (HBV) infection is a global health problem [1], especially in Taiwan [2]. Patients with chronic HBV infection are at an increased risk of developing end-stage liver disease including cirrhosis and hepatocellular carcinoma (HCC) [3]. Previous studies in Taiwan have shown that the higher the serum HBV-DNA levels are at baseline, the higher the cumulative incidence of cirrhosis and HCC over time [4, 5]. Similarly, in a European study of patients with HBV-related compensated cirrhosis, the cumulative probability of hepatic decompensation was lowest in HBeAg-negative patients with undetectable HBV DNA levels compared with HBeAg-negative and HBeAg-positive patients with detectable HBV DNA levels (4 vs. 13 vs. 18 %) [6]. Therefore, the primary goal of chronic hepatitis B (CHB) therapy is to persistently suppress HBV replication, thus preventing the progression of liver disease. In addition, recent studies have also confirmed that antiviral treatment can reduce the risk of HCC and improve the survival of CHB patients [7–11].

Previous studies have reported that suppressing the serum HBV-DNA level to less than 2000 IU/mL was associated with clinical improvements in CHB patients [12–14]. Furthermore, recent studies have suggested that earlier suppression of the HBV DNA to an even lower level during the course of antiviral therapy has a higher likelihood of resulting in improved clinical outcomes [15]. For example, the highest rates of HBeAg seroconversion and lowest rates of drug resistance were observed in a subgroup of patients who achieved serum HBV-DNA levels $<$2000 IU/mL within the first 6 months of lamivudine (LAM) treatment [16]. These findings suggest that an early virologic response is correlated with higher clinical efficacy and a lower risk of drug resistance.

Telbivudine (LdT) is a potent anti-HBV agent with no fetal toxic effects in preclinical studies. CHB patients treated with LdT, including HBeAg-positive and HBeAg-negative patients, demonstrate a significantly greater reduction in serum HBV-DNA levels and lower genotypic resistance than do those treated with LAM [17, 18]. Subgroup analyses of a GLOBE study revealed that the long-term benefit of LdT treatment could be predicted according to baseline clinical characteristics and virologic response at week 24 [19]. In HBeAg-positive patients, improved clinical efficacy and lower drug resistance were observed in those with a baseline serum HBV-DNA level less than 9 $\log_{10}$ copies/mL and a serum alanine aminotransferase (ALT) level greater than two times the upper limit of normal (ULN). By contrast, a baseline serum HBV-DNA level less than 7 $\log_{10}$ copies/mL alone could predict improved treatment results in HBeAg-negative patients. Furthermore, patients who achieved HBV DNA levels less than 300 copies or 60 IU/mL at week 24 of therapy had superior clinical outcomes compared with the entire study population. The question as to whether the positive clinical trial findings can be extrapolated to our clinical practice is not clearly understood; hence, we attempted to validate the efficacy and drug resistance to LdT treatment in CHB patients who had favorable baseline and on-treatment features in a real-life clinical setting.

Methods

This study had an open-label, prospective and retrospective, and multicenter design. Consecutive CHB patients who received LdT treatment were enrolled from July 2009 to September 2011. The inclusion criteria were: (1) males or females aged more than 18 years, (2) clinical history compatible with compensated CHB, and (3) positivity of serum hepatitis B surface antigen (HBsAg) for more than 6 months. The exclusion criteria were: (1) pregnant or nursing female; (2) coinfection with hepatitis C virus (HCV), hepatitis D virus (HDV), or human immunodeficiency virus (HIV); and (3) serum creatinine greater than or equal to 2× the ULN. Data regarding the serum ALT level, HBV DNA level, HBeAg, and/or anti-HBe status were recorded. The treatment of each participant was at the discretion of the treating physicians. In patients who discontinued or changed prescriptions, clinical information was retrieved for an assessment of treatment outcomes. "Super-responders" were defined as HBV DNA levels less

than or equal to 9 $\log^{10}$ copies/mL, ALT greater than or equal to 2× the ULN in addition to polymerase chain reaction (PCR) negativity at week 24 of LdT treatment in HBeAg-positive patients, and HBV DNA levels less than 7 $\log^{10}$ copies/mL in addition to PCR negativity at week 24 of LdT treatment in HBeAg-negative patients. The primary endpoint for the super-responders in the subgroup of HBeAg-positive CHB patients was to achieve HBeAg seroconversion and PCR negativity at week 104 of LdT treatment. The primary endpoint for super-responders in the subgroup of HBeAg-negative patients was to achieve PCR negativity at week 104 of LdT treatment. The virologic response and PCR negativity were defined as HBV DNA levels less than 300 copies/mL after antiviral treatment. The biochemical response was defined as ALT normalization after treatment.

Laboratory testing

The blood and biochemical tests were conducted using routine automated methods (Roche Analytics; Roche Professional Diagnostics, Penzberg, Germany). HBsAg, HBeAg, anti-HBe, and anti-HCV were assayed using an Abbott ARCHITECT i2000 immunoassay analyzer. Serum HBV-DNA levels were measured using an Abbott real-time HBV amplification reagent kit with a sensitivity of 15 IU/mL (51 copies/mL) and linear range of 15–10^9 IU/mL. Elecsys HBsAg II quant immunoassay (ROCHE ANALYTICS; Roche Professional Diagnostics, New Jersey, USA) was performed according to the manufacturer's instructions to quantify serum HBsAg levels. On-board dilution was performed by the analyzer automatically. The range of measurement was 0.05–52,000 IU/mL. Genotypic resistance was confirmed using direct sequencing in patients with virologic breakthroughs.

Statistical analysis

Statistical analysis was performed using SPSS Version 16.0 (SPSS, Inc., Chicago, IL, USA). Data were analyzed using a chi-square test, a student's t-test, Pearson correlation, and multivariate logistic regression analysis as appropriate. All of the tests of significance were two-tailed, and a p value less than 0.05 was considered statistically significant.

Results

Demographic and baseline characteristics

In this multicenter study, a total of 116 CHB patients including 64 HBeAg-positive and 52 HBeAg-negative patients with compensated liver function were enrolled. Among the patients, 89 were males (76.7 %) and 27 were females (23.3 %). The mean age was 41 ± 11 years at enrollment (range: 28–67 years). One patient (0.9 %) had cirrhosis. The mean baseline ALT was 261 ± 289 U/L, and the mean baseline HBV DNA level was 6.72 ± 1.58 $\log_{10}$ IU/mL. Furthermore, the mean level of baseline qHBsAg was 4750 ± 3074 IU/mL. In this study, HBeAg-positive CHB patients had higher serum ALT and HBV DNA levels than did HBeAg-negative CHB patients. In addition, they were also younger than were the HBeAg-negative patients (Table 1).

Flow of the patients through the study

Of the 116 patients, 9 discontinued the treatment prematurely. The causes of the treatment stoppage included loss of follow-up for six patients, a virologic breakthrough in one, and adverse events for two. Of the 107 patients continuing antiviral treatment, 17 switched to other drugs (7 to Tenofovir and 10 to Entecavir). The causes included adverse events in seven patients, genotypic resistance in three, virologic breakthroughs in two, and the decision of treating physicians for five. A total of 14 patients received add-on adefovir treatment because of virologic breakthroughs in 8 cases and genotypic resistance in 6 cases (Fig. 1).

Efficacy of LdT treatment at week 104 in CHB patients with favorable baseline characteristics and PCR negativity at week 24

Of the 64 HBeAg-positive patients, 35 met the criteria of a baseline serum ALT level greater than 2× the ULN and a HBV DNA level less than 9 $\log_{10}$ copies/mL and had complete data from baseline to week 104 of therapy. The rate of PCR negativity at week 24 was 40 % (14/35). Among these 14 super-responders, the rates of virologic, biochemical, and serologic response were 78.6 % (11/14), 64.3 % (9/14), and 50 % (7/14), respectively, at week 104 (Fig. 2). Of the seven patients with HBeAg seroconversion, only one patient stopped LdT by himself after 2 years and 3 months of treatment and was lost to follow-up due to viral relapse (242 copies/mL from an undetectable level). Of the 52 HBeAg-negative patients, 34 met the criteria of a baseline HBV DNA level less than 7 $\log_{10}$ copies/mL and had complete data from baseline to week 104 of therapy. The rate of PCR negativity at week 24 was 85.3 % (29/34). Among these 29 super-responders, the rates of virologic and biochemical responses were 96.6 % (28/29) and 72.4 % (21/29), respectively (Fig. 2a, b).

Table 1 Demographics and baseline characteristics in this study population

	Total ($n = 116$)	HBeAg-positive ($n = 64$)	HBeAg-negative ($n = 52$)	p value	OR (95 %CI)
Age (year)*	41 ± 11 (21–67)	36 ± 9 (21–67)	47 ± 9 (27–66)	<0.001	0.88 (0.84–0.93)
Sex [n (%)]	M, 89 (76.7 %)	M, 48 (75 %)	M, 41 (78.8 %)	0.665	0.80 (0.34–1.93)
Cirrhosis [n (%)]	1/111 (0.9 %)	0/60 (0 %)	1/51 (1.9 %)	0.266	–
ALT (U/L)*	261 ± 289 (34–1802)	311 ± 336 (58–1802)	200 ± 205 (34–1175)	0.039	1.0 (0.99–1.00)
ALT ($\log_{10}$U/L)	2.259 ± 0.343 (1.53–3.26)	2.327 ± 0.359 (1.76–3.26)	2.176 ± 0.305 (1.53–3.07)	0.017	4.05 (1.24–13.25)
ALT > 80 [n (%)]	108/116 (93.1 %)	61/64 (95.3 %)	47/52 (90.4 %)	0.464	2.16 (0.49–9.51)
ALT > 200 [n (%)]	48/116 (41.4 %)	32/64 (50 %)	16/52 (30.8 %)	0.040	2.25 (1.05–4.84)
Genotype B [n (%)]	60/84 (71.4 %)	29/46 (63 %)	31/38 (81.6 %)	0.089	0.56 (0.27–1.18)
Genotype C [n (%)]	24/84 (28.6 %)	17/46 (37 %)	7/38 (18.4 %)	0.089	2.33 (0.88–6.14)
HBV DNA, $\log_{10}$copies/mL*	6.72 ± 1.58 (3.49–9.53)	7.45 ± 1.46 (3.49–9.53)	5.84 ± 1.25 (3.53–8.53)	<0.001	2.43 (1.74–3.40)
qHBsAg (IU/mL)*	4750 ± 3074 (42–16,668)	4385 ± 2986 (147–16,668)	5187 ± 3157 (42–16,254)	0.22	1.0 (0.99–1.00)
qHBsAg ($\log_{10}$IU/mL)	3.518 ± 0.494 (1.62–4.22)	3.521 ± 0.374 (2.17–4.22)	3.513 ± 0.613 (1.62–4.21)	0.935	1.03 (0.44–2.40)
Treatment duration	162 ± 35 (38–223)	162 ± 36 (38–219)	162 ± 34 (50–223)	0.961	0.99 (0.99–1.00)

HBeAg hepatitis B e antigen, *ALT* alanine aminotransferase, *HBV* hepatitis B virus, *DNA* deoxyribonucleic acid, *qHBsAg* quantitative hepatitis B surface antigen, *OR* odds ratio, *CI* confidence interval

PS. * mean (range)

Genotypic resistance of LdT treatment at week 104 in CHB patients with favorable baseline characteristics and PCR negativity at week 24

Of the 14 HBeAg-positive super-responders, virologic breakthrough was noted in 3 (21.4 %), but genotypic resistance was confirmed in 1 (7.1 %; rtM204I plus rtL80 V). Two patients had virologic breakthroughs without genotypic resistance. A possible explanation is the poor adherence to medication. All of them received add-on treatment with adefovir. In Taiwan, the Bureau of National Health Insurance reimburses drugs of add-on treatment for 3 years if virologic breakthrough is confirmed one time in clinical practice. Of the 29 HBeAg-negative super-responders, genotypic resistance was confirmed in 2 (6.9 %; rtV214A, rtM204I; Fig. 2a, b).

Safety and tolerability

Of the 116 patients, 9 (7.8 %) experienced adverse events, 2 discontinued treatment, and 7 switched to other drugs. The adverse events included muscle-related complaints such as pain or weakness in six patients, dizziness in one, insomnia in one, and dysgeusia in one. No severe adverse events were observed during the study period.

Efficacy and genotypic resistance in the study population at baseline, and on-treatment predictors

At week 104 of treatment, the rate of biochemical response was 78.8 % (83.3 % in HBeAg-positive; 77.8 % in HBeAg-negative patients) and the rate of virologic response was 77.8 % (74.4 % in HBeAg-positive; 84.2 % in HBeAg-negative patients). In the HBeAg-positive patients, the rate of HBeAg seroconversion was 29.8 %. The results of a univariate analysis indicated that PCR negativity at week 24 of therapy was the only factor associated with virologic response at week 104. Among the HBeAg-positive CHB patients, those with HBeAg seroconversion had higher baseline serum qHBsAg levels than did those without. The results of the multivariate analysis confirmed the positive association of baseline serum qHBsAg levels (1000 IU/mL per increment) with HBeAg seroconversion at week 104 of LdT treatment (data not shown). Genotypic resistance was confirmed in 15 (12.9 %) patients. Compared with the patients receiving LdT monotherapy without genotypic resistance, PCR negativity at week 24 of therapy was the only factor associated with genotypic resistance (Table 2).

Dynamics of qHBsAg during LdT treatment

A Pearson correlation test showed that the baseline qHBsAg levels were not, overall, correlated with HBV DNA levels in patients (Pearson correlation, $r = 0.097$, and $p = 0.403$). This also holds true for both HBeAg-positive (Pearson correlation $r = 0.033$ $p = 0.84$) and HBeAg-negative patients (Pearson correlation, $r = 0.136$, $p = 0.44$). For HBeAg-positive patients, the mean qHBsAg level significantly increased from baseline to Year 1 and from Year 1 to Year 2 of therapy (paired t test, $p < 0.001$ and $p = 0.011$). If a significant increase of

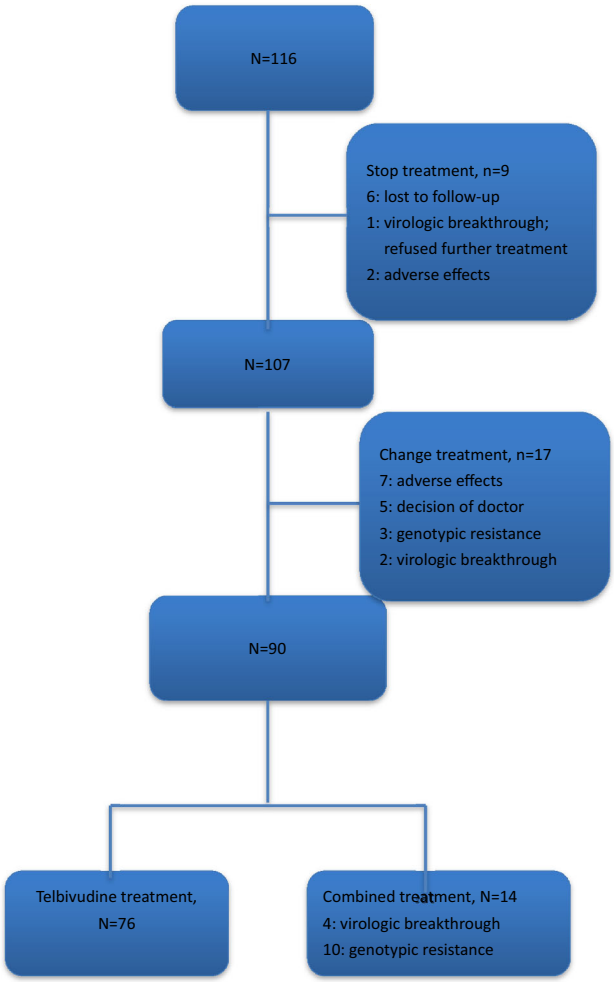

Fig. 1 The flow of patients

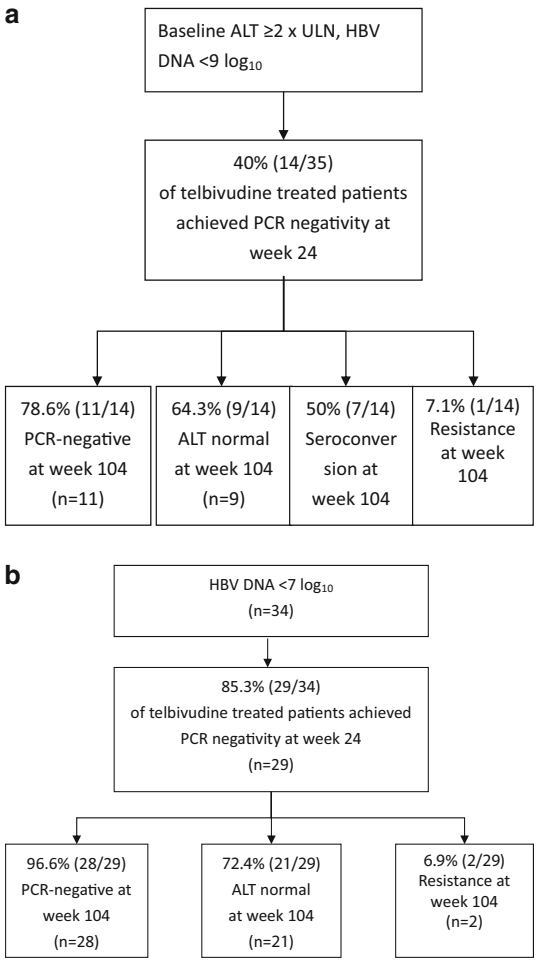

Fig. 2 **a** The efficacy and resistance of telbivudine treatment in HBeA-positive CHB patients with favorable predictors (baseline serum HBV-DNA $\leq$9 log10 copies/mL, ALT $\geq$ 2xULN and 24-week PCR negativity). **b** The efficacy and resistance of telbivudine treatment in HBeA-negative CHB patients with favorable predictors (baseline serum HBV-DNA $\leq$ 7 log10 copies/mL and 24-week PCR negativity)

qHBsAg was defined as a 10 % increase from baseline, 70.5 % (31/44) of the HBeAg-positive patients had a significant increase of qHBsAg at Year 1 of LdT treatment. For the HBeAg-negative patients, although the mean qHBsAg level seemed to slightly increase from baseline to Year 1 and from Year 1 to Year 2 of therapy, no statistical significance was reached (Fig. 3). Among the HBeAg-positive patients, those with HBeAg seroconversion had higher baseline qHBsAg levels than did those without ($p = 0.007$). The mean qHBsAg level had no difference from baseline to year 1 of therapy in HBeAg seroconverters (7497 vs. 7000; paired t test, $p = 0.927$), but increased in HBeAg non-seroconverters (4041 vs. 6077; paired t test, $p = 0.001$). Regarding HBsAg production, previous studies have reported three pathways: the replication, integration, and HBsAg pathways. LdT can effectively suppress the replication pathway, which produces mature infectious virions. The integration and HBsAg pathways produce only HBsAg subviral particles. Thus, increased qHBsAg levels during LdT treatment may be from HBsAg subviral particles rather than mature virions. However, the relationship between HBsAg subviral particles and therapeutic response requires further study.

Discussion

In this multicenter study including 116 LdT-treated CHB patients, both HBeAg-positive and HBeAg-negative super-responders achieved satisfactory virologic, biochemical, and serologic responses at week 104 of therapy. The rate of genotypic resistance was 7.1 % in the HBeAg-positive patients and 6.9 % in the HBeAg-negative patients. In addition, the PCR negativity at week 24 of therapy was the only factor predictive of virologic response and genotypic resistance to LdT treatment. These findings validate the

Table 2 Demographics and baseline characteristics of telbivudine-treated chronic hepatitis B patients categorized by genotypic resistance

	Genotypic resistance ($n = 15$)	No genotypic resistance ($n = 74$)	p value	Crude OR (95 %CI)	Adjust OR (95 %CI)
Age (year)*	40 ± 8 (28–54)	42 ± 11 (21–66)	0.616	0.99 (0.93–1.04)	1.0 (0.95–1.06)
Sex [n (%)]	M, 13 (86.7 %)	M, 57 (77 %)	0.510	1.94 (0.40–9.45)	1.65 (0.32–8.52)
Cirrhosis [n (%)]	0	0	–	–	–
HBeAg-positive [n (%)]	10 (66.7 %)	34 (45.9 %)	0.167	2.35 (0.73–7.56)	–
ALT U/L	227 ± 171 (90–770)	259 ± 2689 (34–1398)	0.661	1.0 (0.99–1.00)	–
ALT$\log_{10}$U/L	2.276 ± 0.258 (1.95–2.89)	2.261 ± 0.344 (1.53–3.15)	0.876	1.15 (0.21–6.13)	–
ALT > 80 [n (%)]	15 (100 %)	69 (93.2 %)	0.584	–	–
ALT > 200 [n (%)]	7 (46.7 %)	30 (40.5 %)	0.776	1.28 (0.42–3.92)	–
HBV DNA $\log_{10}$copies/mL	6.83 ± 1.26 (4.93–9.14)	6.49 ± 1.66 (3.49–9.53)	0.473	1.24 (0.86–1.77)	–
Genotype B [n (%)]	9/12 (75 %)	41/52 (78.8 %)	1.0	1.21 (0.39–3.74)	–
qHBsAg (IU/mL)	4020 ± 2894 (677–7831)	4969 ± 3004 (42–16,254)	0.341	1.0 (0.99–1.00)	–
qHBsAg ($\log_{10}$IU/mL)	3.461 ± 0.403 (2.83–3.89)	3.528 ± 0.537 (1.62–4.21)	0.700	0.79 (0.25–2.55)	–
PCR-negative at week 24 [n (%)]	5/15(33.3 %)	48/70(68.6 %)	0.017*	0.23 (0.07–0.75)	0.23 (0.07–0.79)
Duration of treatment (week)	172 ± 26 (130–219)	165 ± 25 (107–223)	0.397	0.99 (0.97–1.01)	–

HBeAg hepatitis B e antigen, *ALT* alanine aminotransferase, *HBV* hepatitis B virus, *DNA* deoxyribonucleic acid, *qHBsAg* quantitative hepatitis B surface antigen, *PCR* polymerase chain reaction, *OR* odds ratio, *CI* confidence interval

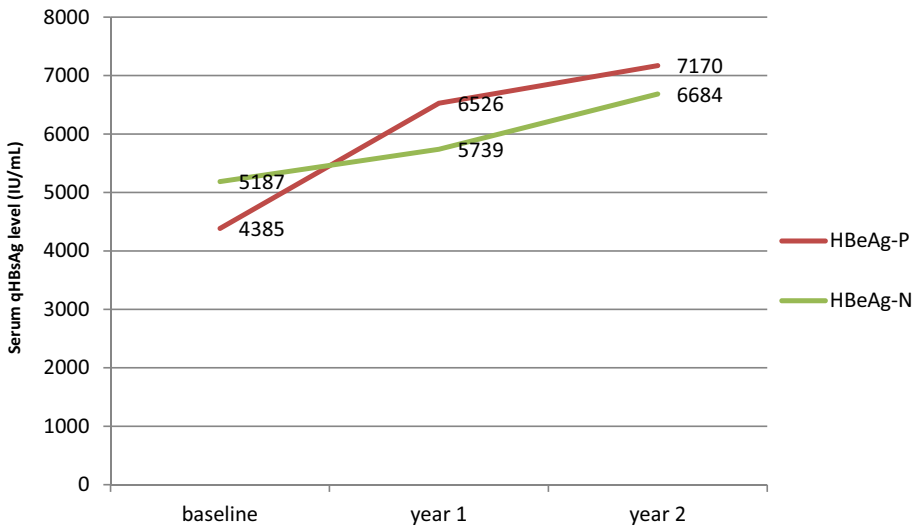

Fig. 3 The dynamic of qHBsAg during telbivudine treatment

concept of "super-responders" to LdT; however, on-treatment monitoring must continue because of the low probability that the super-responders may develop genotypic resistance.

In this real-world study, the super-responders were selected on the basis of baseline characteristics: HBV-DNA levels, ALT levels, and PCR negativity at week 24 of LdT treatment. Although the cut-off of HBV DNA detectability is 51 copies/mL, the PCR negativity was defined as <300 copies/mL in the study, which was the same with the GLOBE study. In our real-world data, the main difference from the GLOBE study was the low rate of PCR negativity at week 24 in HBeAg-positive CHB patients with favorable baseline characteristics (40 vs. 71 %). In another study from Taiwan, the rate of PCR negativity at week 24 was 39 % in the HBeAg-positive CHB patients with favorable baseline characteristics [20], which was consistent with our results. The host genomic background and prevailing HBV genotypes are different between the GLOBE study population and ours, which may explain the different results.

The roadmap concept is mainly focused on on-treatment virologic responses [21, 22]. It was validated to be an

optimized strategy for improving clinical outcomes of antiviral treatment in a recent randomized control study of 606 HBeAg-positive CHB patients receiving LdT treatment [23]. Those with suboptimal responses, defined as HBV DNA levels greater than 300 copies/mL at week 24 of therapy, were randomly divided into two groups: those in one group continued LdT monotherapy and those in the other group received add-on treatment with adefovir. The data showed that the add-on group achieved more favorable virologic responses and less genotypic resistance than did the monotherapy group, suggesting that treatment strategies should be adjusted in suboptimal virologic responders at week 24 of LdT treatment. Other real-world data also confirmed the usefulness of the roadmap concept when add-on treatment was used with adefovir in inadequate virologic responders to prevent genotypic resistance [24]. Our real-world data validated the importance of baseline characteristics and on-treatment virologic responses at week 24 of therapy for the clinical outcomes of LdT-treated CHB patients.

Higher baseline serum ALT and lower serum HBV-DNA levels were correlated with improved therapeutic responses to LdT treatment [25, 26]. A serum HBV-DNA level less than 1000 copies/mL at week 12 was observed to be a more accurate predictor of viral suppression at year 2 of LdT treatment [27]. In patients with partial or inadequate responses at week 24 of LdT treatment, a poor early qHBsAg kinetics (an increase in qHBsAg level >0.4 log IU/mL at week 12) was an early predictor of genotypic resistance in year 2 [24]. Our data confirmed that PCR negativity at week 24 of therapy can predict virologic response and drug resistance to LdT treatment in year 2 and that the baseline qHBsAg level was associated with serological response in the HBeAg-positive patients. However, two of our findings regarding the dynamics of qHBsAg during LdT treatment require additional studies. First, the mean qHBsAg level increased during LdT treatment in the HBeAg-positive CHB patients instead of decreasing in those patients receiving interferon or other antiviral drugs such as entecavir (ETV) [28–30]. Second, the patients with serologic responses had higher baseline qHBsAg levels than did those without.

In the registration trial, LdT had a more favorable virologic response and less genotypic resistance than LAM did. A systemic review also confirmed these findings [31]. Compared with ETV, which bears a high genetic barrier to drug resistance, several meta-analyses indicated that short-term LdT treatment had a more favorable serologic response than ETV, but a higher rate of genotypic resistance [32–34]. Nevertheless, several advantages of LdT such as its safety for pregnant females [35] and improvement of renal function in patients with baseline mild renal dysfunction [36] should not be overlooked. Our data showed that super-responders subjected to LdT treatment had favorable serologic responses, but still had a low rate of genotypic resistance. The question as to whether a dynamic change of qHBsAg can provide further precision in selecting super-responders to LdT treatment requires additional studies.

This study had several strengths. This study was the first to validate the concept of super-responders to LdT. In addition, the HBV genotype and dynamics of qHBsAg during LdT treatment were included for analysis. Furthermore, the baseline qHBsAg level was associated with serologic response, in addition to PCR negativity, at week 24 of LdT treatment. Finally, the signature mutation of LdT resistance was determined in each patient with a virologic breakthrough. However, the limitation is that drug compliance cannot be ascertained in the real-world study.

In summary, at week 104 of LdT treatment, super-responders among HBeAg-positive CHB patients can achieve favorable serologic responses, and super-responders among HBeAg-negative CHB patients can achieve excellent virologic responses. PCR negativity at week 24 of therapy can predict virologic responses and drug resistance in CHB patients in LdT treatment. In addition, the baseline qHBsAg is associated with serologic responses in HBeAg-positive CHB patients.

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Compliance with ethical standards

Conflict and interest Chia-Chi Wang, Chih-Lin Lin, Tsai-Yuan Hsieh, Kuo-Chih Tseng, Cheng-Yuan Peng, Tung-Hung Su, Sheng-Shun Yang, Yu-Chun Hsu, Tsung-Ming Chen and Jia-Horng Kao declare that they have no conflicts of interest.

Human and animal rights All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Taiwan) and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from all patients for inclusion in the study. This article does not contain any studies with animal subjects.

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