Significance of HBV DNA levels at 12 weeks of telbivudine treatment and the 3 years treatment outcome

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Background & Aims: The significance of early HBV DNA suppression during telbivudine treatment in predicting long-term outcomes needs further investigation.

Methods: We determined the cumulative rates of HBeAg seroconversion, ALT normalization, HBV DNA suppression (<12 IU/ml) and telbivudine resistant mutations (using the highly sensitive line probe assay) for 117 treatment-native chronic hepatitis B (CHB) patients (61.5% HBeAg-positive) on telbivudine for 3 years. The significance of serum HBV DNA at week 12 and 24 was compared.

Results: The median age and duration of follow-up were 39 years and 24.2 months, respectively. 117, 105, 69, and 43 patients had been followed up for at least 6 months and 1, 2, and 3 years, respectively. The cumulative rates of HBeAg seroconversion, ALT normalization, HBV DNA undetectability were 46.8%, 80.5%, and 51.2%, respectively, at 3 years. There was an incremental increase in virologic breakthroughs to 39.5% by year 3. Undetectable HBV DNA at week 24 was predictive of favorable long-term outcome. However, the percentage of CHB patients meeting these criteria of favorable baseline profiles is not known. The strongest predictor of a favorable outcome after 2 years is an undetectable serum HBV DNA (<300 copies/ml) at week 24, which is consistent with a previous study on lamivudine [11].

Conclusions: Continuous telbivudine resulted in improved biochemical and virologic outcomes, although there was an incremental increase in cumulative rate of resistance up to year 3. Week 12 HBV DNA of <200 IU/ml was predictive of favorable long-term outcomes.

Introduction

Approximately 400 million people are infected by the hepatitis B virus (HBV) in the world [1]. An elevated serum HBV DNA has been shown to be associated with disease progression, increasing the risk of decompensated cirrhosis and hepatocellular carcinoma (HCC) [2,3]. Current therapy in chronic hepatitis B (CHB) aims at an effective, prolonged suppression of HBV DNA, which would reduce the risk of cirrhosis and HCC [4,5].

Telbivudine is one of the five licensed nucleoside/nucleotide analogs for treatment of CHB. The GLOBE trial compared telbivudine and lamivudine monotherapy in treatment-naive CHB patients, with one-year [6] and two-year results [7] showing a better biochemical, virologic, and histologic response in patients receiving telbivudine. A smaller study in China found similar results [8]. Another trial showed superior viral suppressive effect of telbivudine over adefovir [9]. Further analysis of the GLOBE trial identified baseline characteristics associated with favorable outcomes after 2 years of telbivudine [10]. For hepatitis B e antigen (HBeAg)-positive patients, a baseline HBV DNA of <9 log copies/ml and an alanine aminotransferase (ALT) level of ≥2 times the upper limit of normal (ULN) are predictors of good response. For HBeAg-negative disease, there is a trend for patients with a baseline HBV DNA of <7 log copies/ml developing a better long-term outcome. However, the percentage of CHB patients meeting these criteria of favorable baseline profiles is not known. The strongest predictor of a favorable outcome after 2 years is an undetectable serum HBV DNA (<300 copies/ml) at week 24, which is consistent with a previous study on lamivudine [11].

Antiviral resistance remains a major limitation of telbivudine therapy. The signature mutation associated with telbivudine resistance is M204I, found either alone or together with the secondary mutations L80I/V or L180M [12]. In the GLOBE trial 25.1% of hepatitis B e antigen (HBeAg)-positive patients and 10.8% of HBeAg-negative patients showed genotypic resistance to telbivudine by year 2 [7]. While there are no studies of direct comparison, entecavir [13] and tenofovir [14] have a much better resistance profile, and were preferred agents in different CHB treatment guidelines [15,16].

Various treatment guidelines have also stressed the importance of the HBV DNA level at week 12 to identify patients who are primary non-responders to nucleoside analogs, i.e. failing to achieve more than 1 log decrease of viral load from baseline [15,17,18]. A decrease of viral load by 1 to 3 logs at week 12 was defined as “suboptimal response” by Pawlotsky et al. [19]. Another time point used to define primary non-response is week 24, when the decrease in viral load is less than 2 log [16]. The exact significance of these in telbivudine treatment remains undefined. The significance of week 12 HBV DNA was tested by Zeuzem et al., who concluded that the predictive value was less...
powerful than that of week 24 [10]. However, the usefulness of week 12 HBV DNA in predicting long-term outcomes has also been demonstrated in studies involving other nucleoside analogs [20,21].

The present study aimed to determine the following: (1) the degree of viral suppression of telbivudine in treatment-naive CHB up to 3 years using a highly sensitive HBV DNA assay, (2) the cumulative rate of resistance of telbivudine determined by a sensitive line probe assay, and (3) the usefulness of week 12 and 24 HBV DNA in identifying primary non-responders and predicting long-term outcomes.

Patients and methods

The present study included 117 treatment-naïve patients who received telbivudine 600 mg daily in the Department of Medicine, University of Hong Kong, Queen Mary Hospital, Hong Kong. Of these 117 patients, 64 were recruited from previous trials conducted in our center. The trials included are the GLOBE trial ($n=36$), NV-02B-003 ($n=3$), NV-02B-018 ($n=6$), NV-02C-004 ($n=17$). These patients continued to receive telbivudine in the roller trials NV-02B-010 and NV-02B-022. These trials were funded by Idenix Pharmaceuticals and Novartis Pharmaceuticals. The remaining 53 patients were started on telbivudine monotherapy in our center between July 2007 and December 2009.

All patients were positive for hepatitis B surface antigen (HBsAg) for at least 6 months before treatment. The GLOBE trial recruited both HBsAg-positive and HBsAg-negative patients, while NV-02B-003, NV-02B-018, and NV-02C-004 recruited only HBsAg-positive patients. All trial patients recruited had an elevated serum ALT level of 1.3–10× ULN at their screening visit, and a serum HBV DNA level of at least 6 log copies/ml as determined by the Cobas Amplicor HBV PCR assay (lower limit of quantification 300 copies/ml or 60 IU/ml). The studies were approved by the Institutional Review Board of the University of Hong Kong and the Hospital Authority Hong Kong West Cluster, Hong Kong.

For the patients recruited outside the above mentioned trials, telbivudine was started with the following criteria: (1) elevated ALT levels with HBV DNA levels more than 20,000 IU/ml (1×10⁵ copies/ml) for HBsAg-positive patients without clinical evidence of cirrhosis; (2) elevated ALT levels >ULN with HBV DNA levels >2000 IU/ml (1×10⁴ copies/ml) for HBsAg-negative patients without clinical evidence of cirrhosis; and (3) HBV DNA levels >2000 IU/ml (1×10⁴ copies/ml) for patients with clinical evidence of cirrhosis. Clinical cirrhosis was defined by one of the following: (1) presence of long-term cirrhosis-related complications including ascites (with or without spontaneous bacterial peritonitis), varices, encephalopathy and/or (2) ultrasonographic evidence of small-size liver with or without ascites and splenomegaly. Patients with the following concomitant conditions were excluded: hepatitis C and D infection, Wilson’s disease, autoimmune hepatitis, primary biliary cirrhosis, and significant intake of alcohol (20 grams per day for female; 30 grams per day for male).

Patients were followed up every 3 to 4 months. HBsAg, HBsAb, and antibody to HBeAg (anti-HBe) were tested by enzyme linked immunosorbant assay (ELISA), Abbott Laboratories, Chicago, IL. Liver biochemistry and alpha-fetoprotein (AFP) were measured at every follow-up. HBV DNA levels were determined at baseline, 12 weeks, 24 weeks, and every year after commencing telbivudine. The HBV DNA levels were measured by Cobas Taqman assay (Roche Diagnostics, Branchburg, NJ) with a lower limit of quantification of 60 copies/ml (12 IU/ml) and a linear range of upper detection limit of 6.4×10⁵ copies/ml (1.3×10⁶ IU/ml). For results exceeding the upper detection limit, HBV DNA levels were re-measured after a 100,000-fold dilution. Primary non-response was defined by the serum HBV DNA levels exceeding the upper detection limit, HBV DNA levels were re-measured after a 100,000-fold dilution. Primary non-response was defined by the serum HBV DNA levels exceeding the upper detection limit, HBV DNA levels were re-measured after a 100,000-fold dilution. Primary non-response was defined by the serum HBV DNA levels exceeding the upper detection limit, HBV DNA levels were re-measured after a 100,000-fold dilution. Primary non-response was defined by the serum HBV DNA levels exceeding the upper detection limit, HBV DNA levels were re-measured after a 100,000-fold dilution.

Virologic breakthrough was defined by either an increase of serum HBV DNA by at least 1 log copies/ml from the nadir for patients with detectable viral load, or serum HBV DNA >100 copies/ml (20 IU/ml) for patients with undetectable viral load during telbivudine treatment. Viremic mutational analysis was performed by a line probe assay (LIPA) [Innomogenics NV, Gent, Belgium] [22]. LIPA DR version 2 was used to identify the amino acids at the codons of r80A, r173G, r180A, r181G, rt204A, and rt236A.

All statistical analyses were performed using SPSS version 16.0 (SPSS Inc., Chicago, Illinois). Mann–Whitney U-test was used for continuous variables with a skewed distribution. Pearson’s chi squared test, or Fisher’s exact test when appropriate, was used for categorical variables. Cumulative rate of development of viral resistance was calculated from the formula: $P = 1 - (1 - n/N)(1 - n/2).$ - (1 – n/N) [19].

Results

The baseline demographics of the 117 patients are listed in Table 1. Over 60% of the patients were males (60.7%) and HBeAg-positive (61.5%). The median duration of follow-up was 24.2 months (range 6.0 to 59.8 months). All patients were followed up for at least 6 months, while 105 (89.7%), 69 (59.0%), and 43 (36.7%) were followed up for 1, 2, and 3 years, respectively, at the time of writing. Two patients defaulted follow-up after 6 months of therapy.

The cumulative serologic, biochemical, and virologic outcomes are shown in Fig. 1. The cumulative HBsAg seroconversion rates were 31.9%, 40.9%, and 46.8% from year 1 to 3. There were no cases of HBsAg seroconversion. The cumulative ALT normalization rate peaked at year 2 (88.7%) before decreasing to 80.5% at year 3. The cumulative rate of undetectable HBV DNA showed a similar trend, peaking at 68.1% at year 2 before decreasing to 51.2% at year 3. There was an incremental increase of virologic breakthroughs, from 5.7% at year 1 to 39.5% at year 3.

Concerning the viral mutational analysis, there were no patients with telbivudine resistant mutations at baseline and week 24. Twenty-one patients developed the telbivudine resistant mutation of M204I at different time points during the study period: 5 patients (4.8%) at year 1, 9 patients (13.0%) at year 2 and 7 patients (16.3%) at year 3. The cumulative rates for the development of telbivudine resistance were 4.8%, 17.6%, and 34.0% for year 1, 2, and 3, respectively (Fig. 1). The secondary mutations of L80I/V and L180M were also detected in 71.4% and 23.8%, respectively, by year 3.

The significance of week 12 and 24 serum HBV DNA levels was examined. The median serum HBV DNA at week 12 and week 24 was 3.10 log copies/ml (range: 1.80–4.64 log copies/ml) and 2.59 log copies/ml (range: 1.80–5.37 log copies/ml), respectively. The median decrease of viral load from the baseline for week 12 and 24 was 4.71 log copies/ml (range: 1.37–10.35 log copies/ml) and 5.24 log copies/ml (range: 0.68–10.53 log copies/ml), respectively. At week 12, all patients achieved at least 1 log decrease in viral load; 22 patients (18.8%) achieved an undetectable HBV DNA. At week 24, 75 patients (64.1%) achieved an undetectable HBV DNA; 1 patient had a decrease in viral load of less than 2 log and was later found to have poor drug compliance. Therefore, there were no cases of primary non-response to telbivudine regardless of whether it was assessed at week 12 or 24.
The relationship between the degree of HBV DNA reduction from baseline at week 12 and 24 with the outcomes at year 3 is depicted in Table 2. There was no statistical significant difference between the degree of HBV DNA reduction and HBV DNA undetectability and resistance at year 3.

The significance of the absolute HBV DNA levels at week 12 and 24 is depicted in Table 3. Forty-two percent (29 out of 69) and 32.6% (14 out of 43) with a follow-up period of 2 and 3 years, respectively, had a week 12 HBV DNA of <1000 copies/ml (<200 IU/ml). Week 12 HBV DNA level of <1000 copies/ml was predictive of a favorable long-term response (Fig. 2), with patients having a higher chance of achieving undetectable HBV DNA and a lower chance of developing resistance at both 2 years (p≤0.001 and p=0.016, respectively) and 3 years (p=0.022 and p=0.001, respectively). HBeAg-positive patients achieving week 12 HBV DNA <1000 copies/ml had similar year 2 favorable outcomes (Fig. 2). The probability of undetectable HBV DNA and viral resistance at year 3 was 78.6% and 0%, respectively, for patients with HBV DNA <1000 copies/ml, compared to 44.8% and 51.7%, respectively, for patients with HBV DNA ≥1000 copies/ml at week 12.

33.3% (23 out of 69) and 16.3% (7 out of 43) achieving undetectable HBV DNA (<60 copies/ml or <12 IU/ml) at week 24 were followed up for 2 and 3 years, respectively (Fig. 3). Undetectable HBV DNA at week 24 remained predictive of profound viral suppression up to year 2, but with an inferior odds ratio when compared to week 12 (Table 3). HBeAg-positive patients had similar findings up to year 2 (Fig. 3). The predictability at week 24 for undetectable HBV DNA at year 3 became insignificant. There was a trend for fewer patients to develop genotypic resistance by year 2 and 3.

The outcome of patients with favorable baseline parameters proposed by Zeuzem et al. [10] is shown in Fig. 4. All HBeAg-positive patients with favorable baseline parameters achieving either a week 12 HBV DNA of <1000 copies/ml or a week 24 undetectable HBV DNA did not develop resistance at year 2. For HBeAg-negative patients, 7.8% and 10% of those with favorable baseline parameters and corresponding favorable HBV DNA responses at week 12 and 24, respectively, developed telbivudine resistance at year 2.

Two patients (1.7%) developed myalgia, with symptoms arising after 16 and 21 months of treatment, with a respective creatinine kinase (CK) level of 1771 U/L and 327 U/L. Both patients were switched to entecavir 0.5 mg daily with subsequent resolution of the symptoms of myalgia and normalization of CK levels. There were no other adverse events.

**Discussion**

Previous studies on telbivudine employed HBV DNA assays with a lower limit of quantification of 300 copies/ml, and used direct sequencing techniques for the detection of genotypic resistance [6–9]. The present study employed highly sensitive methods of measurement for both viral load and resistance profile. For serum HBV DNA levels, we employed the Cobas Taqman assay with a lower limit of quantification of 60 copies/ml (12 IU/ml). Therefore, the present study showed the capability of telbivudine in suppressing the viral load to an extremely low HBV DNA level. Viral mutational analysis in previous studies [6–9] using sequencing techniques, could only detect the presence of mutants when there is at least 20–30% of them circulating in the total viral population [23,24]. However, LiPA is able to detect the presence of mutants as long as they have constituted 5% of the total viral population [23,24]. The present study employed highly sensitive methods of measurement for both viral load and resistance profile. For serum HBV DNA levels, we employed the Cobas Taqman assay with a lower limit of quantification of 60 copies/ml (12 IU/ml). Therefore, the present study showed the capability of telbivudine in suppressing the viral load to an extremely low HBV DNA level. Viral mutational analysis in previous studies [6–9] using sequencing techniques, could only detect the presence of mutants when there is at least 20–30% of them circulating in the total viral population [23,24]. However, LiPA is able to detect the presence of mutants as long as they have constituted 5% of the total viral population, and can detect mutations in over 20% of cases not detected by sequencing [22]. Using this sensitive assay in the present study should enhance the accuracy in determining the incidence of resistance.

Currently, most long-term data on telbivudine are based on the two-year results of the GLOBE trial [7]. Hsu et al. [25] and Jia et al. [26] followed up patients from the GLOBE trial and

<table>
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<tr>
<th>Serum HBV DNA reduction</th>
<th>Number of patients</th>
<th>Year 3</th>
<th>Year 3</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Undetectable</td>
<td>Resistance</td>
</tr>
<tr>
<td>&lt;4 log</td>
<td>11 (25.6%)</td>
<td>4 (36.4%)</td>
<td>6 (54.5%)</td>
</tr>
<tr>
<td>≥4 log</td>
<td>32 (74.4%)</td>
<td>18 (56.3%)</td>
<td>9 (28.1%)</td>
</tr>
<tr>
<td>&lt;5 log</td>
<td>21 (48.8%)</td>
<td>10 (47.6%)</td>
<td>10 (47.6%)</td>
</tr>
<tr>
<td>≥5 log</td>
<td>22 (51.2%)</td>
<td>12 (54.5%)</td>
<td>5 (22.7%)</td>
</tr>
<tr>
<td>&lt;6 log</td>
<td>29 (67.4%)</td>
<td>15 (51.7%)</td>
<td>12 (41.4%)</td>
</tr>
<tr>
<td>≥6 log</td>
<td>14 (32.6%)</td>
<td>7 (50.0%)</td>
<td>3 (21.4%)</td>
</tr>
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The values for <3 log reduction are not shown above due to the small number of patients in each group (2.3% for both week 12 and week 24).
another study in China [8] for 3 and 4 years, respectively. Both showed telbivudine obtaining a high rate of viral suppression and ALT normalization. However, only patients without genotypic resistance at the end of their core studies were enrolled. To our knowledge, our study would be the first with 3-year data on continuous telbivudine for CHB patients.

The cumulative rates of HBeAg seroconversion and ALT normalization from the present study were comparable to those observed in previous studies [6–9] up to year 2. In the present study, HBeAg seroconversion and ALT normalization rates up to year 3 were 46.8% and 80.5%, respectively. However, HBV DNA undetectability dropped from 68.1% at year 2 to 51.2% at year 3. Virologic breakthroughs also increased from 26.1% at year 2 to 39.5% at year 3. The cumulative resistance of telbivudine was up to 34.0% at year 3, which is a substantial level even though it was less than that of lamivudine [4]. Although the interpretation of this 3-year resistance data is limited by the small patient sample and the lack of direct comparison with other nucleoside analogs, the use of LiPA instead of sequencing for viral mutational analysis would suggest the sensitivity for resistance in this present study is actually improved. This may be the reason for the finding of a considerably high rate of resistance (34% at year 3) in the present study.

Four patients achieving a favorable week 12 or 24 HBV DNA and undetectable HBV DNA at year 2 developed a low viremic state (115, 135, 136, and 563 copies/ml, respectively) at year 3.

<table>
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<th>Table 3. Significance of week 12 and 24 HBV DNA absolute levels in predicting year 2 and year 3 outcomes.</th>
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<tr>
<td>Week 12 HBV DNA &lt;1000 copies/ml</td>
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<tr>
<td>Undetectable HBV DNA</td>
</tr>
<tr>
<td>Undetectable HBV DNA</td>
</tr>
<tr>
<td>Genotypic resistance to telbivudine determined by line probe assay.</td>
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</tbody>
</table>

Fig. 2. The outcome of 69 patients based on the different achievable HBV DNA levels at week 12. Number of HBeAg-positive patients denoted in italics. Undetectable HBV DNA defined as <60 copies/ml (<12 IU/ml).
despite having no resistance detected (Figs. 2 and 3). It remains a possibility that LiPA failed to detect the mutant virus at such a low viral load. According to the internal validation performed by the manufacturer, the lower limit of application range for test is 990 copies/ml[27]. A continued follow-up of the patients' viral loads would be mandatory for the possibility of the development of resistance.

The concept of primary non-response, defined as a reduction of viral load of less than 1 log from baseline at week 12, was proposed for the early identification of nucleoside analog treatment failure [17]. This concept has been adopted by the guidelines from the European Association for the Study of the Liver (EASL) [15] and the roadmap concept proposed by Keeffe et al. [18]. The guidelines from the American Association for the Study of Liver Diseases (AASLD) adopt a decrease in viral load of less than 2 log at week 24 as the definition of primary non-response [16]. However, the actual prevalence of patients with primary non-response to nucleoside analogs is unknown. In our present study,
with the exception of 1 patient with poor drug compliance, there were no cases of primary non-responders among all 117 patients regardless of which time point used. It would seem that, except for adefovir [28], primary non-response among nucleoside analogs is a rare event.

A defined log reduction in HBV DNA had been previously suggested to be used as a predictive marker of antiviral treatment efficacy [17]. However, the results of our study (Table 2) do not support this approach, despite considering the HBV DNA levels of week 12 or 24. Instead, an absolute serum HBV DNA threshold at baseline or during nucleoside analog treatment has a better predictive value of long-term outcomes [4,10,11]. Our study suggests to use the absolute week 12 HBV DNA level of <1000 copies/ml (<200 IU/ml) for the identification of patients likely to have favorable long-term outcomes. A cut-off value of <1000 copies/ml had previously been used in studies concerning lamivudine [11]. We used a value of <1000 copies/ml of HBV DNA as a cut-off level for week 12, a more liberal value compared to the use of HBV DNA undetectability (<300 copies/ml by Cobas Amplipcr) by Zeuzem et al. [10]. In our study, at week 12 only 18.8% achieved HBV DNA undetectability whereas 42% had HBV DNA levels <1000 copies/ml. Using the cut-off HBV DNA level of <1000 copies/ml, the chance of HBV DNA undetectability at 2 and 3 years was 93.1% and 78.6%, respectively, with no patients developing resistance at 3 years. Therefore, using <1000 copies/ml as a marker for week 12 would target a larger population, allowing more patients with favorable long-term outcomes to be identified.

Similar to other studies [10,11], our study showed an undetectable HBV DNA (<60 copies/ml or <12 IU/ml) at week 24 to be predictive of a favorable long-term viral suppression. However, the odds ratio is inferior to that obtained at week 12 (10.4 versus 18.3, respectively). The failure of achieving statistical significance using week 24 HBV DNA to predict HBV DNA undetectability at year 3 and the borderline p values to predict chance of drug resistance at year 2 and 3 is probably related to the limited number of patients. In spite of this limitation, all the analyses done using week 12 HBV DNA remained statistically significant. It further supports the superiority of using week 12 to week 24 to predict long-term outcome for telbivudine treatment. Another advantage of using week 12 for assessment is that clinicians would not need to wait until week 24 to decide if alternative treatment is needed, although there was no drug resistance detected at week 24 in our study. With respect to lamivudine, a week 4 serum HBV DNA is already predictive of long-term response [29]. This may also hold true for a similar drug like telbivudine, although confirmation by further studies would be needed.

In addition, we found that the combination of baseline HBV DNA and ALT levels with either week 12 or 24 HBV DNA levels can predict zero resistance for HBeAg-positive patients at year 2 (Fig. 4). The combined approach for HBeAg-negative disease was also able to identify patients with favorable outcomes up to year 2, with week 12 HBV DNA levels having a slightly better predictive value than week 24. Therefore, week 12 HBV DNA of <1000 copies/ml has a clinical role in predicting favorable outcomes using this combined approach. However, it should be noted that the analyses were performed on small number of patients. This is likely to be the reason for the finding of less favorable predictive power for drug resistance in HBeAg-negative patients.

Despite an inferior resistance profile compared to entecavir or tenofovir, telbivudine is available at a relatively low price in Asia. A cost-effective analysis in Asia has found telbivudine to be more cost-effective than entecavir or tenofovir in HBeAg-positive disease, and to have comparable cost-effectiveness when compared to tenofovir in HBeAg-negative disease [30]. The cost-effectiveness of telbivudine may be further improved if the factor of week 12 HBV DNA levels is taken into account, making telbivudine a feasible option, although confirmation by further cost-effective analysis would be needed.

In this study, the incidence of myopathy, characterized by myalgia and elevation of CK levels, was 1.7%. This was similar to the quoted figures of 1.1–1.4% from previous studies [31,32]. CK levels poorly predict the onset of myopathy, and should not be merely used for the detection of muscle-related adverse events without a proper clinical assessment.

The main limitation of this study was the limited number of patients with 3 years of follow-up. Because of this limitation, we were not able to report the detailed long-term outcomes for HBeAg-positive and HBeAg-negative patients separately, although HBeAg-positive patients had favorable outcomes up to year 2 for both time points at week 12 and 24. Another limitation is the lack of HBV genotypic data. Since the resistance profiles were determined by a reverse hybridization assay (LiPA), and not by direct sequencing, viral sequence for determination of genotype is not possible.

In conclusion, continuous telbivudine resulted in improved biochemical and virologic outcomes up to year 2, although year 3 data show an incremental increase in the cumulative rate of resistance. A week 12 HBV DNA of <1000 copies/ml (<200 IU/ml) can identify patients with favorable long-term outcomes. Week 12 can be adapted as the first time point in the evaluation of the efficacy of telbivudine, allowing treatment decisions to be made before the development of genotypic resistance.

Conflict of interest

The authors have declared that they received an unrestricted grant from Novartis in order to carry out their research in this manuscript.

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References

Research Article


