Durability of Telbivudine-Associated Improvement of Renal Function Following Withdrawal or Switching of Antivirals in Chronic Hepatitis B Patients

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**Background.** Besides antiviral activities against hepatitis B virus (HBV), telbivudine has an extrahepatic pharmaceutical effect: to improve renal function assessed by estimated glomerular filtration rate (eGFR). However, the durability of this effect after withdrawal of telbivudine or switching to other antivirals has never been investigated.

**Methods.** We conducted a postmarketing, real-world observation study for telbivudine treatment. The durability of telbivudine-associated renal function improvement was examined following withdrawal/switching of antivirals.

**Results.** Of 160 telbivudine-treated, chronic hepatitis B patients, 21, 6, and 2 patients were lost to follow-up, dead, and pregnant during the study, respectively. Of the remaining 131 patients, 26, 47, 28, and 30 patients experienced telbivudine withdrawal, continuous use of telbivudine, switching to entecavir, or switching to tenofovir, respectively. During the first 2 years, eGFR in telbivudine-treated patients significantly improved before withdrawal/switching of antivirals ($P = .009$). Thereafter, eGFR remained unchanged for $>1$ year in the withdrawal ($P = .100$) and continuous use ($P = .517$) subgroups, but decreased significantly in the switching to entecavir ($P = .002$) and switching to tenofovir ($P < .001$) subgroups. Multivariate logistic regression analysis revealed that switching to tenofovir and poor liver functional reserve were predictors for eGFR deterioration.

**Conclusions.** Telbivudine-associated renal function improvement was durable after withdrawal or continuous use of telbivudine. However, renal function deteriorated if patients were switched to entecavir or tenofovir.

**Keywords.** creatine kinase; telbivudine; virological breakthrough.

Hepatitis B virus (HBV) chronically infects 350 million individuals, representing an estimated 5% of the worldwide population [1]. In their lifetime, approximately 15%–40% of chronic hepatitis B patients develop life-threatening complications, such as liver cirrhosis and hepatocellular carcinoma (HCC) [2, 3]. The prevalence of HBV infection varies in different parts of the world. The highest prevalence is found in Asia, Africa, the Middle East, the Mediterranean region, South America, and the Pacific Islands, where the disease is commonly acquired in early childhood [4–6]. The risk of developing chronic HBV infection after acute exposure ranges from 90% in newborns of hepatitis B e antigen (HBeAg)–positive mothers to <5% in immunocompetent adults [7, 8]. There is strong evidence supporting the view that the risk of cirrhosis and liver failure increases with higher serum levels of HBV DNA [9–13]. Hence, the goal of antiviral therapy for chronic hepatitis B is to provide prolonged suppression of HBV replication to abrogate progression of liver injury [14–18].

Currently, interferon α-2b, pegylated interferon α-2a, and 5 oral agents—adefovir dipivoxil, entecavir (ETV), lamivudine, telbivudine, and tenofovir (TDF)—have been approved as therapeutic agents for chronic hepatitis B [19–30]. Telbivudine has been approved for clinical use based on a phase III clinical trial [31, 32]. It is a synthetic thymidine nucleoside analog with a potent inhibitory effect on HBV DNA polymerase. Interestingly, recent studies have indicated that this antiviral drug could improve renal function during long-term usage [33]. The present study is a postmarketing, open-label, prospective, and observational surveillance study for the clinical use of telbivudine in Taiwan. All patients were treated according to the best judgments of their physicians in outpatient clinics without interference by this study. Treatment was continued, stopped, or switched to other antivirals at the physician’s discretion. The clinical efficacies, virological suppression or breakthrough, side effects, and renal function changes were assessed.

**METHODS**

**Inclusion/Exclusion Criteria**

This study was approved by the Institutional Review Board at Chang Gung Medical Center (98-3808C, 98-3663B). Written

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informed consent was obtained from all enrolled patients. Patients must have met all of the following criteria to be included in this observational study: (1) male or female at least 18 years of age; (2) documented chronic hepatitis B defined by all of the following: clinical history compatible with chronic hepatitis B, detectable serum hepatitis B surface antigen (HBsAg) >6 months at screening visit, with either HBeAg positive or negative; (3) willing and able to comply with the observational drug regimen subscribed by the physicians and all other study requirements; (4) willing and able to provide written informed consent to participate in the study. Patients were excluded from the study for any of the following reasons: (1) pregnancy, intent to become pregnant, or breastfeeding; (2) co-infection with hepatitis C virus, hepatitis D virus, or human immunodeficiency virus; (3) 1 or more known primary or secondary causes of liver disease other than hepatitis B (eg, alcoholism, steatohepatitis, autoimmune hepatitis, malignancy with liver metastasis, hemochromatosis, alpha-1 antitrypsin deficiency, Wilson’s disease, other congenital or metabolic conditions affecting the liver, congestive heart failure or other severe cardiopulmonary disease); (4) enrolled or planning to be enrolled in another clinical trial of an investigational agent while participating in this study; (5) unable to receive safety and tolerability assessments.

Patients were considered lost to follow-up (ie, those patients whose status was unclear because they failed to appear for study visits without stating an intention to withdraw) if no particular reason could be documented after the attempts were made to contact the patients.

Duration of Observation Study
The term of prospective observation was 104 weeks (24 months). Subsequent renal function data beyond 24 months were assessed in a retrospective manner. Dose adjustments, interruptions, or changes of medication were entirely clinically judged by physicians. In the case of HBeAg seroconversion at any point, treatment was continued or stopped at the clinician’s discretion. Virological breakthrough (defined as an increase in HBV DNA load by 1 Log10 from nadir) was either continuously treated with telbivudine (patient remained in the observational study) or by the addition of other antiviral agents to the patient’s regimen or by switching to other treatments at the physician’s discretion.

Safety
All of the adverse events contained in the medical chart were extracted and recorded for the safety assessment.

Statistical Analysis
For a surveillance study, descriptive statistics were used for presenting characteristics of efficacy variables. Mean, standard deviation, median, minimum, maximum, and 95% confidence interval were presented for continuous variables. Categorical variables were summarized by counts and percentages in frequency tables. All statistical assessments used were 2-sided, and P < .05 was considered statistically significant. Continuous variables were analyzed using the t test. The Wilcoxon rank-sum or sign-rank test was conducted if the data were not normally distributed. Categorical variables were analyzed using the chi-square or Fisher exact test.

RESULTS
Patients Included
Overall, 160 patients could be classified into 6 groups according to their clinical presentations (Table S1). HBeAg was positive in 39 patients. They were classified into 3 groups: group I, HBeAg-positive, treatment-naïve patients (n = 16); group II, HBeAg-positive and ETV experienced patients (n = 15); and group III, HBeAg-positive and HCC patients receiving chemotherapy (n = 8). None of these patients had taken nephrotoxic drugs. Other baseline characteristics were listed in Table S1.

The HBeAg-negative patients (n = 121) could also be divided into 3 groups: group IV, HBeAg-negative, treatment-naïve patients (n = 39); group V, HBeAg-negative, liver cirrhotic patients (n = 34); and group VI, HBeAg-negative, HCC or other cancer patients, receiving chemotherapy (n = 48). In this group of patients, 45, 2, and 1, respectively, had HCC, breast cancer, and gastric cancer.

Compliance, Withdrawal, Switching Antivirals, and Loss to Follow-up
During the time of this study, antiviral therapy was covered by the National Health Insurance Policy of Taiwan for only a 2-year period. At the end of the second year of postmarketing observation, 7 patients achieved a complete virological response with complete virological suppression for more than 1 year (the stopping rule), and the treatment was stopped. Six patients died of HCC, 21 patients were lost to follow-up, and 2 had pregnancy (Figure 1). Of 58 patients switching to other antivirals during or at the end of the 2-year period, 28 were switched to ETV and 30 to TDF. The decision of withdrawal/switching was made by the physicians after discussion with the patients. In the remaining 66 patients, telbivudine was still being used at the end of the second year. Afterward, 19 met the stopping rule of treatment and were withdrawn from antivirals. On the other hand, 38 and 9 patients continued the telbivudine treatment for >1 year and <1 year, respectively, until the end of this study (Figure 1). Three of them received an adefovir add-on treatment due to development of drug resistance.

Therapeutic Responses
Table S2 summarizes the virological, biochemical, and serological responses of the patients. The virological response rates as assessed by HBV DNA copy number of fewer than 300 copies/mL were lower in the groups that were HBeAg-positive (groups I and II) compared with the groups that were HBeAg-negative (groups IV, V, and VI) at week 48 of surveillance. The response rates in group III were not assessed due to the small case number and the short patient survival time. At week 104,
Increased Serum Creatine Kinase Levels

No severe adverse events were associated with telbivudine use. Even in 2 pregnancies, both infants were delivered smoothly and without birth defects. Table S3 listed the adverse events of grades 1 and 2. Muscle soreness (11.25%) and abdominal distension (11.88%) were reported in more than 10% of patients. Muscle soreness could have been associated with a high creatine kinase (CK) level. We also examined the biochemical and hematological data during the follow-up visits. Table S4 shows that a significant proportion of patients experienced a high CK level. The median CK levels were significantly higher at week 104 than at baseline. The upper limit of normal in the central laboratory of the hospital was 200 IU/mL, suggesting that in groups I and V, more than half of the patients had abnormal CK levels. Notably, the highest CK level reached greater than 1000 IU/mL in group V patients. Univariate followed by multivariate analysis showed that liver cirrhosis (P = .008) and body height (P = .0167) were independently associated with a high (>300 IU/mL) CK level (Table S5).

Improvement of eGFR and Durability After Withdrawal/Switching Antivirals

We assessed the eGFR using both the Cockcraft-Gault and the Modification of Diet in Renal Disease (MDRD) methods (Table S6). The statistical analysis employed the paired t test for all patients combined (calculated by the MDRD method) (Figure 2, B and C). For all patients who were followed until 24 months (n = 131), including those who had switched antivirals during this period, a significant increase in the eGFR level was found between baseline and week 104 (P = .024), and an even more significant increase was observed between weeks 48 and 104 (P < .001).

Because the national insurance coverage period for antiviral therapy was 2 years during our study period, another analysis was performed by comparing the baseline eGFRs with those assessed at the time of withdrawal (n = 7) or the end of 2-year continuous telbivudine (n = 66), or the time of switching antiviral treatment (n = 58) (paired t test for all these patients combined). In this analysis, all patients had received telbivudine...
treatment only during the comparison period (Figure 3A). It was found that eGFR increased significantly during the telbivudine treatment period \( (P = .009) \). However, when compared with the final eGFRs assessed >1 year into the mid–time point, the eGFRs decreased significantly (between initial eGFRs and final eGFRs, \( P = .010 \); between mid–time point eGFRs and final eGFRs, \( P < .001 \)) (Figure 3A).

To understand why the overall renal function deteriorated when compared with the initial level, we performed a subgroup analysis (Figure 3B and C). It was found that in patients switching to ETV or TDF, eGFR significantly deteriorated after switching \( (P = .002 \) and \(<.001\), respectively) (Figure 3B). On the other hand, in patients who continued to use telbivudine for >1 year or in patients withdrawn from telbivudine treatment, the eGFRs did not change \( (P = .100 \) and \(.517\), respectively) (Figure 3C).

When analyzing eGFR improvement from the beginning of treatment to the end of insurance coverage (Table S7), it was found that HCC, previous use of contrast medium, initial eGFR, CKD-II, hemoglobin, prothrombin time, albumin, and bilirubin \( (P < .001, .001, .013, .033, <.001, .003, <.001, .008, \) respectively) were predictors in univariate analysis; whereas only albumin \( (P = .011) \) remained an independent predictor in multivariate analysis, suggesting that liver functional reserve was important for eGFR improvement. On the other hand, when analyzing eGFR improvement from the beginning of treatment until >1 year after the end of insurance coverage (Table S8), it was found that HCC, withdrawal of telbivudine, switching to

![Figure 2](https://example.com/image2.png)

**Figure 2.** (A) Kaplan-Meier analysis of virological time-to-breakthrough between HBeAg-positive patients (blue), HBeAg-negative patients (green), and HCC patients (orange). (B) Changes in renal function (mean ± SD) assessed by eGFR (MDRD method) by group. Groups I to III are HBeAg-positive, light green, blue, and black, respectively. Groups IV to VI are HBeAg-negative, red, deep green, and orange, respectively. (C) Changes in renal function assessed by eGFR (MDRD method) for all patients enrolled (paired t tests). Abbreviations: HBeAg, hepatitis B e antigen; HCC, hepatocellular carcinoma; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease.
Stages of Chronic Kidney Disease and eGFR Improvement

When classified by stages of CKD, 113, 38, 5, and 4 patients were in CKD-I, II, III, and IV, respectively. When compared between patients in CKD-II vs other stages, 26/38 (68.4%) vs 59/122 (48.4%) patients showed improvement of eGFR at the end of insurance coverage for telbivudine (P = .030). This observation was consistent with those of previous studies. After withdrawal or switching antivirals, when compared between patients in CKD-II vs non-II stages, 21/38 (55.3%) vs 48/122 (39.3%) patients showed improvement of eGFR >1 year after the end of insurance coverage (P = .084). When classified according to withdrawal, continuous use of telbivudine, switching to entecavir, and switching to tenofovir, none of the subgroups showed significant differential eGFR improvement between CKD-II vs non-II patients, possibly due to a small case number in each subgroup. However, if the latter 2 switching subgroups were combined (n = 58), improvement of eGFR could be found in 10/17 (58.8%) vs 12/41 (29.3%) for CKD-II vs non-II patients (P = .035).

DISCUSSION

This was a prospective, postmarketing surveillance study. No intervention to the therapeutic decision was allowed during the follow-up assessments. As a result, about half of the patients enrolled did not continue the telbivudine antiviral treatment.
Virological breakthrough, noncompliance, and abnormal CK levels with muscle soreness were the major known reasons for withdrawal or switching. Another limitation of this study was the short survival time of the HCC or cancer patients receiving chemotherapy.

As reported in previous global studies [18, 31, 32], the virological suppression effect remained excellent in telbivudine-treated patients. The median HBV DNA levels were below the detection limit in all HBeAg-negative groups and were 0.0051 and 0.0002 Meq/mL for HBeAg-positive (groups I and II) patients. Despite the excellent virological suppression effect, virological breakthrough due to resistant mutants remained a significant concern [18, 31, 32]. In non-HCC patients, the virological breakthrough rates ranged from 8.7% to 25.0% among the different groups at week 104, which is compatible with other reports [18, 31]. Surprisingly, no virological breakthrough was observed in HCC patients receiving chemotherapy in this study. The difference was statistically significant when compared with the HBeAg-positive patients. The reason for this finding was not clear. We speculate that a low baseline viral load could be a contributing factor. Additionally, the para-cancerous cirrhotic liver had already experienced many rounds of hepatocyte regeneration, which might not have allowed vigorous HBV replication, and thus was less favorable to the development of resistant mutants.

When adverse events were investigated, we found that muscle soreness was a major complaint from the patients. When such an event was combined with a high CK level, the physicians would likely switch the patients to other oral antiviral agents. Logistic regression analysis showed that high CK levels were most likely associated with liver cirrhosis and taller body height. To our knowledge, this finding has not been previously reported.

Recent studies have indicated that long-term use of telbivudine was associated with an improvement in renal function [33]. In this study, we examined the eGFRs at baseline, week 48, and week 104. Improvement in the eGFR occurred mostly during the second year of telbivudine treatment. Here we further analyzed the changes of eGFR following different phases of antiviral treatments. Strikingly, in 26 patients who withdrew from telbivudine treatment, eGFR assessed >1 year later showed no significant changes, indicating that telbivudine-associated renal function improvement was quite durable. In contrast, in patients switching to ETV or TDF, eGFRs deteriorated significantly. Recently, an independent study also showed that withdrawal of telbivudine treatment, eGFR assessed >1 year later showed no significant changes, indicating that telbivudine-associated renal function improvement was quite durable. In contrast, in patients switching to ETV or TDF, eGFRs deteriorated significantly. Recently, an independent study also showed that withdrawal of telbivudine treatment, eGFR assessed >1 year later showed no significant changes, indicating that telbivudine-associated renal function improvement was quite durable. In contrast, in patients switching to ETV or TDF, eGFRs deteriorated significantly. Recently, an independent study also showed that withdrawal of telbivudine treatment, eGFR assessed >1 year later showed no significant changes, indicating that telbivudine-associated renal function improvement was quite durable. In contrast, in patients switching to ETV or TDF, eGFRs deteriorated significantly. Recently, an independent study also showed that withdrawal of telbivudine treatment, eGFR assessed >1 year later showed no significant changes, indicating that telbivudine-associated renal function improvement was quite durable. In contrast, in patients switching to ETV or TDF, eGFRs deteriorated significantly. Interestingly, in 26 patients who withdrew from telbivudine treatment, eGFR assessed >1 year later showed no significant changes, indicating that telbivudine-associated renal function improvement was quite durable. In contrast, in patients switching to ETV or TDF, eGFRs deteriorated significantly. Interestingly, in 26 patients who withdrew from telbivudine treatment, eGFR assessed >1 year later showed no significant changes, indicating that telbivudine-associated renal function improvement was quite durable. In contrast, in patients switching to ETV or TDF, eGFRs deteriorated significantly.

In summary, this study showed that the efficacy, adverse reaction, drug resistance, and renal function improvement of telbivudine usage in Taiwan were all consistent with those found in global studies. Additionally, we discovered that the renal function improvement attributed to telbivudine usage was quite durable after withdrawal, whereas the renal function could deteriorate if switching to other drugs.

Supplementary Data
Supplementary materials are available online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Author contributions. Chao-Wei Hsu and Chau-Ting Yeh contributed equally to the acquisition of the data, analysis, and interpretation of the data, and statistical analysis and drafting of the manuscript. The other authors contributed to establishing the study concept, recruiting patients, and revision of the manuscript.

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