Potential Benefit of Telbivudine on Renal Function Does Not Outweigh Its High Rate of Antiviral Drug Resistance and Other Adverse Effects


Five nucleos(t)ide analogs (NUCs) are approved for the treatment of hepatitis B. NUC therapy had been shown to reverse fibrosis and cirrhosis, and to reduce the risk of hepatic decompensation and hepatocellular carcinoma.1,2 Although NUCs are effective in suppressing hepatitis B virus (HBV) replication, they do not eradicate the virus; therefore, most patients require long-term treatment. Long-term efficacy, safety, drug resistance, and costs are the major considerations in determining which NUC should be considered as first-line treatment.

NUCs are generally safe and well-tolerated, but side effects have been reported including nephrotoxicity, neuropathy, myopathy, lactic acidosis, and decrease in bone mineral density.1,2,3,6 Of these, nephrotoxicity associated with adefovir or tenofovir has received the most attention. Nephrotoxicity manifesting as decrease in glomerular filtration rate (GFR) is more common in patients who are >50 years old, have baseline renal insufficiency, hypertension and/or diabetes mellitus.7 Proximal renal tubular injury—resembling Fanconi syndrome with hypophosphatemia, hypouricemia, aminoaciduria, and glycosuria—had also been reported.8 In most instances, nephrotoxicity is reversible after dose reduction or discontinuation of treatment. The postulated mechanisms of nephrotoxicity associated with adefovir and tenofovir treatment include increased intracellular influx through organic anion transporters and/or a defect in its luminal excretion through multidrug-resistance–associated proteins, or mitochondrial toxicity in the proximal tubular cells of the kidney.7 Lamivudine and entecavir have not been reported to be associated with nephrotoxicity. All NUCs approved for HBV are eliminated by the kidneys and dose reduction or discontinuation of treatment. The postulated mechanisms of nephrotoxicity associated with adefovir and tenofovir treatment include increased intracellular influx through organic anion transporters and/or a defect in its luminal excretion through multidrug-resistance–associated proteins, or mitochondrial toxicity in the proximal tubular cells of the kidney.7 Lamivudine and entecavir have not been reported to be associated with nephrotoxicity. All NUCs approved for HBV are eliminated by the kidneys and dose adjustments are needed in patients with impaired renal function. Renal impairment is common in patients with compensated cirrhosis and in liver transplant recipients. Therefore, renal safety is an important factor in deciding which NUC is most appropriate for patients with hepatitis B, particularly those who have other risk factors for renal impairment.

References

Editorial

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In this issue of the *Gastroenterology*, Gane et al\textsuperscript{10} reported the results of a comprehensive analysis of renal function in the telbivudine clinical trial database. This database included 1367 patients with compensated chronic hepatitis B randomized to receive telbivudine or lamivudine for 2 years in the GLOBE study, 655 patients in the GLOBE study and in a similar study in China (Study 015) who received telbivudine in the feeder study and in the extension study (A2303) for a total duration up to 4 years, 70 patients who continued to receive telbivudine in another extension study (CN04E1) for a total duration of 4–6 years, 66 patients who discontinued telbivudine treatment at the end of the GLOBE study or Study 015 owing to efficacy, 398 patients who received lamivudine in the GLOBE study and telbivudine for 2 years in the extension study (A2303), and 228 patients with decompensated cirrhosis randomized to receive telbivudine or lamivudine for 2 years in Study A2301.\textsuperscript{6,11–14}

Renal function was assessed by 3 different calculations for estimated GFR (eGFR), Cockroft-Gault, Modification of Diet in Renal Disease, and Chronic Kidney Disease Epidemiology Collaboration. The authors showed that renal function assessed by serum creatinine and the 3 formulas for eGFR improved in patients who received telbivudine during the GLOBE trial, whereas those who received lamivudine had a decline in renal function. The changes in eGFR at the end of 2 years of treatment were +8.5% versus −0.5% for the entire cohort of patients who received telbivudine versus lamivudine, respectively; +11.4% versus −2.4% for patients age ≥50 years; +17.2% versus +4.3% for those with eGFR ≤90 mL/min/1.73 m\textsuperscript{2} at baseline; and +7.2% versus +2.3% for patients with cirrhosis. Multivariate analysis of baseline factors in the GLOBE study that predicted a shift in eGFR from baseline of 60–90 to ≥90 mL/min/1.73 m\textsuperscript{2} at year 2 were telbivudine treatment (odds ratio [OR], 2.51), younger age (OR, 0.94), and non-Caucasian race (OR, 0.34). Improvement in eGFR was maintained during long-term telbivudine treatment. At year 4, mean increase of eGFR was +14.9 mL/min/1.73 m\textsuperscript{2} and 74% (165/223) of the telbivudine-treated patients with baseline eGFR of 60–89 mL/min/1.73 m\textsuperscript{2} had eGFR of ≥90 mL/min/1.73 m\textsuperscript{2}.

Among the patients who received lamivudine in the GLOBE/015 studies with no evidence of genotypic resistance at the end of the feeder studies, eGFR improved by 8.9% after 2 years of lamivudine and by 9.5% after 2 years of telbivudine treatment in the extension studies.

In patients with decompensated cirrhosis, eGFR at year 2 improved by 2.0 mL/min/1.73 m\textsuperscript{2} in the patients who received telbivudine but declined by 4.6 mL/min/1.73 m\textsuperscript{2} in those who received lamivudine.

The study by Gane et al\textsuperscript{10} showed that improvement in eGFR was observed in chronic hepatitis B patients treated with telbivudine. The improvement in eGFR was maintained during continuous treatment of telbivudine for up to 6 years and was observed in various subpopulations. Although the mechanism responsible for the improvement in renal function is unclear, the results are convincing.

What are the implications of these results? Is the improvement in renal function specific for telbivudine? Does the benefit on renal function outweigh the risk of antiviral resistance and other adverse effects of telbivudine? Should telbivudine be recommended as a first-line antiviral agent for hepatitis B?

Gane et al\textsuperscript{10} showed that improvement in eGFR was observed in the telbivudine group but not in the lamivudine group in the GLOBE study; however, in the subgroup of patients in GLOBE/015 studies who did not have genotypic resistance after 2 years of lamivudine, an improvement in eGFR was observed and the percentage of change in eGFR was similar to that observed after 2 years of telbivudine treatment in the extension studies. Thus, although the authors found that improvement in eGFR during telbivudine treatment was not related to virologic response, it is possible that a higher rate of virologic breakthrough in the lamivudine group in the GLOBE study might have contributed to the minor decline in eGFR in the entire lamivudine group.

Improvement in renal function has not been systematically examined in patients receiving other HBV NUCS. Registration trials and clinical studies have focused on the incidence of renal impairment (Table 1).\textsuperscript{1,3,5,14–22} Renal impairment was reported in studies of other HBV NUCs, but not in studies of telbivudine. Reports of some telbivudine trials provided data on improvement in eGFR but did not specify whether any patient had deterioration in renal function.\textsuperscript{6,11–14} Renal impairment is more commonly associated with adefovir than with other HBV NUCs and more common in patients with decompensated cirrhosis than in those with compensated liver disease.\textsuperscript{5,15–18,22} Despite their similarities in molecular structure, nephrotoxicity is less common with tenofovir treatment than with adefovir treatment, occurring in 1% of patients with HBV monoinfection and compensated liver disease after ≤5 years of tenofovir treatment.\textsuperscript{1} A retrospective, match-control study comparing 230 patients with chronic hepatitis B who had received 2 years of telbivudine or entecavir treatment showed that, compared with baseline, serum creatinine and eGFR improved significantly in both groups after 1 year of treatment but no significant difference was observed in either group at year 2.\textsuperscript{2} Similarly, a shift toward a better eGFR category was seen in both groups at year 1 but not at year 2.

The key question is whether improvement in renal function outweighs the risk of antiviral drug resistance and other adverse effects of telbivudine to justify its use as a first-line antiviral agent for hepatitis B. Despite its potent antiviral activity, telbivudine has a low barrier to antiviral drug resistance and shares similar resistance mutations as lamivudine. A phase III clinical trial of telbivudine found that viral resistance was observed in 25.1% and 39.5% of hepatitis B e antigen (HBeAg)-positive patients and in 10.8% and 25.9% of HBeAg-negative patients after 2 years of telbivudine and lamivudine, respectively.\textsuperscript{6} Of the patients who did not have genotypic resistance at year 2 and who continued to receive telbivudine in the extension study, the cumulative rate of antiviral resistance at 4 years was 10.6% in HBeAg-positive and 10.0% in HBeAg-negative patients.\textsuperscript{13} By contrast, phase III trials of entecavir and tenofovir in nucleoside-naïve patients showed genotypic resistance rates
Table 1. Renal Safety of Approved Nucleos(t)ide Analogs for Chronic Hepatitis B and Dose Adjustments According to Renal Function

<table>
<thead>
<tr>
<th>Mechanisms of renal excretion</th>
<th>Lamivudine</th>
<th>Adefovir</th>
<th>Entecavir</th>
<th>Telbivudine</th>
<th>Tenofovir</th>
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<tr>
<td>Glomerular filtration:</td>
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<tr>
<td>Active secretion</td>
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<td>(organic cationic transport system)</td>
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<tr>
<td>Glomerular filtration:</td>
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<tr>
<td>Active tubular secretion</td>
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<tr>
<td>Net tubular secretion</td>
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<tr>
<td>Presumably passive diffusion</td>
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<tr>
<td>Glomerular filtration:</td>
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<tr>
<td>Active tubular secretion</td>
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Incidence of nephrotoxicity in patients with compensated liver disease,\(^b\) %
- After 1 year of treatment: NA
- During long-term treatment (year of assessment):
  - Lamivudine: 0.5 (%) (3)
  - Adefovir: 3-9.2 (%) (5)
  - Entecavir: 1.6 (%) (2)
  - Telbivudine: NA
  - Tenofovir: 1 (%) (5)

Incidence of nephrotoxicity in patients with decompensated cirrhosis (year of assessment),\(^b\) %
- Lamivudine: NA
- Adefovir: 6 (1)-24 (2)
- Entecavir: 4.5 (1)-17 (2)
- Telbivudine: NA
- Tenofovir: 8.9 (%) (1)

Recommended dose adjustment according to renal function\(^c\)

<table>
<thead>
<tr>
<th>GFR, mL/min</th>
<th>Lamivudine</th>
<th>Adefovir</th>
<th>Entecavir</th>
<th>Telbivudine</th>
<th>Tenofovir</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥50</td>
<td>100 mg/d</td>
<td>10 mg/d</td>
<td>0.5 mg/d</td>
<td>600 mg/d</td>
<td>300 mg/d</td>
</tr>
<tr>
<td>30-49</td>
<td>100 mg first dose, then 50 mg/d</td>
<td>10 mg every 48 hours</td>
<td>0.25 mg/d or 0.50 mg every 48 hours</td>
<td>600 mg every 48 hours</td>
<td>300 mg every 48 hours</td>
</tr>
<tr>
<td>10-29</td>
<td>35 mg first dose, then 15-25 mg/d</td>
<td>10 mg every 72 hours</td>
<td>0.15 mg/d or 0.50 mg/week</td>
<td>600 mg every 72 hours</td>
<td>300 mg every 72-96 hours</td>
</tr>
<tr>
<td>Dialysis</td>
<td>35 mg first dose then 10 mg/d</td>
<td>10 mg every 7 days (following dialysis)</td>
<td>0.05 mg/d or 0.50 mg/week (following dialysis)</td>
<td>600 mg every 96 hours (following dialysis)</td>
<td>300 mg/week or after a total of approximately 12 hours of dialysis</td>
</tr>
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</table>

GFR, glomerular filtration rate; NA, data not available.
\(^a\)Data obtained from product monographs.
\(^b\)Renal impairment was defined as an increase in serum creatinine by ≥0.5 mg/dL and confirmed by 2 consecutive laboratory results in references 3, 5, 15-22; serum creatinine increase from baseline by ≥0.5 mg/dL and serum creatinine clearance <50 mL/min in references 1 and 3; definition of renal impairment was not provided in references 6, 13, and 14, time dependent changes in eGFR by Modification of Diet in Renal Disease (MDRD) in reference 13, and by MDRD and Chronic Kidney Disease Epidemiology Collaboration in reference 14.
\(^c\)For lamivudine-refractory patients; 1 mg/d if GFR ≥50 mL/min, 0.5 mg/d or 1 mg every 48 hours if GFR 30-49 mL/min, 0.3 mg/d or 1 mg every 72 hours if GFR 10-29 mL/min, 0.1 mg/d or 1 mg every 7 days if on dialysis.
at 5 years of 1.2% and 0%, respectively. In an attempt to decrease the rate of antiviral resistance, the roadmap approach was tested in a prospective study of 100 HBeAg-positive patients. Patients with detectable HBV DNA at week 24 were to receive add-on tenofovir and 45% did so. The high percentage of patients in whom tenofovir had to be added as a rescue therapy by week 24 negates its benefit of being a lower cost HBV NUC. Telbivudine has been associated with myopathy and peripheral neuropathy and these adverse events were more frequent and severe when telbivudine was used in combination with pegylated interferon, leading to early termination of that trial. In patients who received 4 years of telbivudine monotherapy, muscle symptoms (including myalgia, muscular weakness, musculoskeletal pain, myopathy, myositis, and musculoskeletal discomfort), peripheral neuropathy, and grade 3–4 increase in serum creatine kinase levels were observed in 6.1%, 1.2%, and 15.9% of patients, respectively.

In summary, although Gane et al provided tantalizing data suggesting that telbivudine may be renal protective, it is not clear whether this protective effect is specific to telbivudine. This potential benefit does not outweigh the high rate of antiviral drug resistance and neuromuscular adverse effects. Therefore, these results, albeit being highly relevant from the clinical and safety profile perspectives, do not support the use of telbivudine as a first-line NUC in hepatitis B treatment and should not prompt revision to existing guidelines.

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**References**


A New Comorbidity Model for Predicting Mortality in Patients With Cirrhosis: Does It Work?

Patients with chronic liver disease often have major comorbidities that can affect their survival and healthcare resource utilization, as well as patient-reported outcomes such as their health-related quality of life.\textsuperscript{1-3} In clinical and epidemiologic research, controlling for comorbidities associated with chronic liver disease is critical for any analysis that assesses predictors of these outcomes or interventions that are designed to improve them. Historically, accounting for comorbidities in patients with liver diseases required inclusion of a specific comorbid condition such as severe pulmonary disease or using a generic comorbidity score such as Charlson Comorbidity Index (CCI). One could argue that these approaches are suboptimal to accurately measure the impact of comorbidities on important clinical and patient reported outcomes. This is particularly important because these approaches can be very general and do not identify the effect of each variable in the model on the particular disease process of interest, but rather only the cumulative effect. Without knowing which variables may have the most influence on the outcome of interest, it becomes hard for practitioners to direct care appropriately.\textsuperscript{4-16}

In this issue of \textit{Gastroenterology}, Jepsen et al reported on a new scoring system in their article, “Development and validation of a comorbidity scoring system for patients with cirrhosis.”\textsuperscript{17} The authors’ intent was to develop a Cirrhosis-Specific Comorbidity Scoring System (CirCom) to help determine how comorbidities may contribute to mortality as well as to compare the CirCom with the generic but very popular CCI. After logistic regression analysis using data from the Danish Patient Registry, there were 9 comorbidities (chronic obstructive pulmonary disease, acute myocardial infarction, peripheral arterial disease, epilepsy, substance abuse other than alcoholism, heart failure, non-metastatic or hematologic cancer, metastatic cancer, and chronic kidney disease) that comprised the final CirCom score. The investigators subsequently tested their score on 2 separate cohorts of patients (Aarhus alcoholic cirrhosis cohort and a nationwide cohort of patients with chronic hepatitis C viral infection) using the Net ReClassification Index (NRI) comparing the mortality results with the mortality results obtained with the CCI. They determined that the CirCom score had a higher C statistic (Harrell’s) and NRI values than the CCI and was easier to use. The authors concluded that CirCom may be the preferred method for controlling comorbidities that could influence survival of patients with cirrhosis. Furthermore, this score could be beneficial for clinical research and epidemiologic studies of patients with cirrhosis. In fact, they consider that since the NRI has a more intuitive interpretation and greater sensitivity when strong predictors (Model for End Stage Liver Disease [MELD] score and alcohol consumed) are part of the model, the CirCom score can reclassify 10\%–15\% of cirrhosis patients to a better prognostic class including patients with compensated cirrhosis where the chance of death from cirrhosis remains small.\textsuperscript{7}

The authors should be congratulated on this novel approach and for the development of a new prognostic tool for a population that consumes many healthcare dollars and remains among the top 15 causes of death.\textsuperscript{18,19} Although the tool is easy to use, measuring the burden of comorbidity by just 2 conditions, there are a few concerns about how this tool was developed. First, the concept of “active” as opposed to “inactive” diagnosis can be different for different diseases. For instance, myocardial infarction diagnosed 8 days ago is more likely to be truly “inactive” compared with metastatic cancer. The fact that inactive metastatic cancer was not associated with mortality (adjusted hazard ratio, 1.33; [95\% confidence interval, 0.97–1.82]) does suggest that a large proportion of those with inactive diagnosis were, in fact, in remission, but mixing active/inactive diagnosis concepts in acute and chronic conditions seems to measure different aspect of prognosis.

Even though the statistical methods used to verify the score in other populations were novel and thought provoking, the results obtained using NRI as an analytic tool or “gold standard” may be questionable. The NRI is a new method.

Conflicts of interest
The authors have made the following disclosures: Anna S. Lok had received research grants from Bristol-Myers Squibb, Gilead, and Merck, and had served as advisor for Gilead, GlaxoSmithKline, and Merck. The remaining author discloses no conflicts.

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