Effectiveness of Tenofovir Alafenamide in Chronic Hepatitis B Patients with Normal Alaine Aminotransferase and Positive Hepatitis B Virus DNA

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Received: 4 April 2021 | Revised: 26 April 2021 | Accepted: 11 May 2021 | Published: 15 June 2021

Abstract

Background and Aims: With an increasing understanding of hepatitis B, the antiviral indications have been broadening gradually. To evaluate the effectiveness of tenofovir alafenamide (TAF) in chronic hepatitis B (CHB) patients with normal alanine aminotransferase (ALT) and detectable hepatitis B virus (HBV) DNA, those who are ineligible for broader antiviral criteria from the Chinese CHB prevention guide (2019). Methods: A total of 117 patients were recruited and their data were collected from paper or electronic medical records. HBV DNA and liver function were measured at baseline and throughout the 24-week follow-up. The effectiveness end-point was complete virological response. The safety endpoint was the first occurrence of any clinical adverse event during the treatment. Results: Among the 117 patients, 45 had normal ALT as well as detectable HBV DNA and they were not recommended for antiviral therapy according to Chinese Guidelines (2019). After TAF antiviral therapy, the rates of patients who achieved HBV DNA <20 IU/mL at 4, 12 and 24 weeks were 77.1%, 96.7% and 96.8% respectively. Among them, the undetectable rates of HBV DNA in patients with low baseline viral load at 4, 12 and 24 weeks were 92.3%, 100% and 100%, while the rates of those with high baseline viral load were 68.2%, 94.1% and 94.4%. Compared with 71.4%, 94.4% and 94.7% in the high baseline group, the undetectable rates of HBV DNA at 4, 12 and 24 weeks in the low baseline liver stiffness group were 85.7%, 100% and 100%. There was no statistical significance among the above groups. Conclusions: CHB patients who had normal ALT and detectable HBV DNA and did not meet “CHB prevention guide (2019)”, could achieve complete virological response in 24 weeks after antiviral treatment by TAF.

Introduction

Approximately 2 billion people worldwide are infected with hepatitis B virus (HBV), in which 257 million people suffer from chronic hepatitis B (CHB) according to the World Health Organization. In China, the reported prevalence of HBV surface antigen (HBsAg) in the general population ranged from 5-6%, and there are 20 to 30 million cases of CHB. The guidelines of the Asia-Pacific Society of Hepatology Clinical Registration Survey (commonly known as CLCS) shows that the HBV infection rate among patients with liver cancer is as high as 92.05%. Considering the situation where China has the largest population and heaviest disease burden in the world, the threat of hepatitis B is expected to remain a huge challenge for the next 10 years. In 2019, the Chinese Society of Hepatology updated its CHB prevention and treatment guidelines and broadened antiviral therapy indication, in which a portion of patients with normal alanine aminotransferase (ALT; ≤40 U/L) and some risk factors or complications are recommended to receive antiviral therapy. But, is this sufficient enough? Do we still leave out some patients that should be treated? Can CHB patients with normal ALT benefit from universal antiviral treatment?

When it comes to whether to initiate antiviral treatment for CHB patients with normal ALT, there is no unified consensus by the major association CHB guidelines currently. The guidelines of the Asia-Pacific Society of Hepatology (2015) and the America Society of Hepatology (2018) did not recommend antiviral treatment for these patients, without the evidence of liver biopsy. However, there existed some different viewpoints from the guidelines of European Society of Hepatology (2017) as well as that of Chinese Society of Hepatology (2019). Based on these two guidelines, experts argued that patients with a family history of HBV-related liver cirrhosis or cancer should receive antiviral therapy regardless of whether or not the evidence of he-
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Fig. 1. Flowchart of selecting patients in this cohort study. *Antiviral indications are recommended from the Guidelines for the Prevention and Treatment of Chronic Hepatitis B in China (2019). For patients with normal ALT and detectable HBV DNA, it is recommended to initiate antiviral therapy if following risk factors exist: (1) liver biopsy results of G2 and/or S2 stage or above; (2) older age than 30 years, with a family history of liver cirrhosis or HCC; (3) older age than 30 years, and a noninvasive diagnosis technique or liver biopsy having suggested obvious liver inflammation or fibrosis; and (4) HBV-related extrahepatic manifestations. **According to the guidelines in China, the HBV DNA of CHB patients in the immune control phase is less than 2,000 IU/mL, so it is set as cut-off value to make subgroup analysis.

Methods

Patient selection and study design

A total of 117 confirmed CHB patients were recruited from the Union Hospital of Huazhong University of Science and Technology from May 1, 2019 to June 30, 2020. These patients met all the following inclusion criteria: (1) aged from 18 to 65 years; (2) never treated with other anti-HBV nucleos(t)ide analogs within 1 year before enrollment; (3) without family history of hepatic cirrhosis or carcinoma; (4) meet the CHB diagnostic criteria of the guidelines: ALT ≤40 U/L, liver stiffness measurement (LSM) <9.0 kPa, HBV DNA detectable (in our hospital: upper limit of normal of HBV DNA of 20 IU/mL); and (5) followed up for at least 24 weeks. We excluded patients who met one of the following criteria: (1) confirmed diagnosis of liver cirrhosis, primary liver cancer or liver metastasis; (2) coinfected with hepatitis A virus, hepatitis C virus, hepatitis D virus, hepatitis E virus or human immunodeficiency virus; or (3) combined with other chronic liver diseases, such as alcoholic liver disease, drug-induced liver disease or autoimmune liver disease, etc. Finally, a total of 45 patients were enrolled and divided into several subgroups based on their HBV DNA (IU/mL) level or LSM respectively. Among them, 18 patients with HBV DNA between 20 ∼ 2,000 IU/mL were regarded as the low viral load group, while 27 patients with HBV DNA ≥2,000 IU/mL were selected as the high viral load group. Besides, 18 patients with LSM <6.0 kPa and 27 patients with 6.0 ≤LSM <9.0 kPa were enrolled as low LSM and high LSM groups respectively. All the applicable patients received tenofovir alafenamide (TAF) to initiate antiviral therapy based on their own discretion after being fully informed of the costs, effectiveness, safety and long-term risks of persistent positive HBV DNA. Clinical data were collected at 4, 12 and 24 weeks after antiviral treatment initiation. Please refer to the flowchart (Fig. 1) for more details. This research protocol was approved by the Ethics Committee of the Union Hospital Affiliated to Tongji Medical College of Huazhong University of Science and Technology (Lot No. UHCT-IETC-SOP-016-03-01), and conducted in compliance with the Declaration of Helsinki. The requirement for informed consent was waived by the Ethics Committee.

Measurements

Patients were assessed by physical examinations, blood biochemical and virological parameters, hepatobiliary imaging
(ultrasonography, computerized tomography or magnetic resonance) tests, and HBV at baseline and weeks 4, 12 and 24 respectively. Serum HBV DNA level was detected by real-time fluorescent quantitative polymerase chain reaction system (purchased from Xi’an Tianlong Technology Co., Ltd.; lower limit of detection: 20 IU/mL). Serum biochemical index included ALT, aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (γ-GGT), total bilirubin (TBIL), direct bilirubin (DBIL), albumin (ALB), globulin (GLB). The above indexes were detected by the QLYMPU-AU5400 biochemical analyzer (Olympus, Japan). LSM was performed through transient elastography (FibroTouch, HISKY, China) by experienced operators. No obvious liver inflammation or fibrosis was noted when the LSM was <9.0 kPa, and fatty liver was diagnosed when the liver fat attenuation was >240 dB/m.

Outcomes

The primary endpoint was complete virological response (CVR), defined as serum HBV DNA <20 IU/mL after antiviral treatment. Secondary assessments included the following: (1) degree of serum HBV DNA levels decreased in patients with detectable HBV DNA; (2) level of blood biochemical after antiviral treatment; and (3) incidence of any clinical adverse event during TAF treatment.

Statistical analysis

All statistical analyses were performed using SPSS version 26.0 (IBM Corp., USA). Quantitative variables with normal distribution were expressed with the mean±standard deviation (SD) and were compared by t test, and those with non-normal distribution were expressed with median (interquartile range, IQR) and compared by Wilcoxon rank-sum test. Categorical variables were demonstrated with frequency and percentage, which were compared by chi-squared test or Fisher’s exact test. All statistical tests were two-tailed, and p value of <0.05 was considered to be statistically significant.

Results

Overall effectiveness of CHB patients with normal ALT who were ineligible to the antiviral indications of guidelines

A total of 117 CHB patients were screened, and 45 patients (31 males and 14 females) were eligible and enrolled in the study (Fig. 1). All these patients were treated with TAF once a day (Vemlidy 25 mg Gilead Science, Inc., USA). Their mean age was 43.8±9.2 years, mean ALT level was 24.2±8.8 U/L, and median HBV DNA was 3.65 (2.87–4.21) log IU/mL. They had no family history of hepatic cirrhosis or HCC, and no obvious inflammation or fibrosis by transient elastography as well, with mean LSM of 6.4±1.4 kPa. The primary effectiveness assessment in the study was CVR (complete virological response) rate with TAF at different timepoints. The overall undetectable rates of HBV DNA were 77.1%, 96.7% and 96.8% at 4, 12 and 24 weeks respectively (Fig. 2) after the treatment with TAF. None of those patients showed complete disappearance of serum HBsAg and change of hepatitis B e antigen (HBeAg) during the 24-week follow-up. The treatment was well tolerated with no severe adverse events in most cases (Table 1). Next, we made a subgroup analysis to explore whether baseline HBV viral load or LSM would affect the virologic response rate.
we are missing out on these patients who need to be treated.

In addition, a significant proportion of normal-ALT CHB patients actually do not meet any of antiviral treatment indications but they still have high risk of progression of disease after long-term follow-up. A Korean study of 1,931 CHB patients\textsuperscript{12} found that, compared with treated patients with ALT ≥2× the upper limit of normal, untreated patients with normal ALT had a higher incidence of HCC and a higher mortality rate of liver transplantation. Another study of 1,965 CHB patients in the immune tolerance phase found that the cumulative incidence of liver cirrhosis was as high as 15%\textsuperscript{13} after 11.5 years of follow-up. Besides, a meta-study of 830 CHB patients with normal ALT found that 20.7%\textsuperscript{14} of the patients had significant liver fibrosis (≥F2) with no connection to HBV DNA level, HBeAg status, age, family history, etc. Therefore, there is an urgent need to determine whether universal antiviral therapy is effective and safe for normal ALT CHB patients who are ineligible for the antiviral indications of 2019 China guidelines.

**Loosening antiviral indications is a tendency**

First of all, universal antiviral therapy in our study was safe and effective in normal ALT CHB patients. Specifically, virological response in the low viral load group was quite favorable. The HBV DNA undetectable rate was higher than 90% at 4 weeks and even reached up to 100% in 12 weeks. No major safety issues or serious adverse reactions were observed during follow-up. Although it seemed that the virological response rate in the high viral load group was lower than the low, the difference was not statistically significant. Moreover, the virological response rates were getting closer and closer between the two groups as the therapy time prolongs. So, we have reason to believe that initiating TAF antiviral therapy is effective for these patients who are ineligible for the antiviral indications of 2019 China guideline, as long as the treatment period is sufficient enough. In addition, we observed an interesting phenomenon in the high viral load group. Only one HBeAg positive patient whose baseline

| Table 2. Baseline data for CHB patients with different viral loads |
|-------------------|------------------|-----------------|-----------------|
| **Low viral load (20 ≤HBV DNA <2,000 IU/mL)** | **High viral load (HBV DNA >2,000 IU/mL)** | **Low stiffness (LSM <6.0 kPa)** | **High stiffness (6.0 kPa ≤LSM <9.0 kPa)** |
| Sex ratio, male: female | 10: 8 | 21: 6 | 0.115 | 13: 5 | 18: 9 | 0.693 |
| Age in years | 45.0±7.8 | 43.0±10.1 | 0.482 | 43.3±11.0 | 44.2±8.0 | 0.760 |
| TB in μmol/L | 13.8 (11.4, 23.0) | 15.3±5.7 | 0.799 | 15.6±6.4 | 13.7 (11.8, 21.2) | 0.917 |
| DB in μmol/L | 5.1 (4.2, 7.9) | 4.9 (4.2, 7.3) | 0.451 | 5.0 (4.4, 7.6) | 4.9 (4.2, 7.5) | 0.676 |
| ALT in U/L | 21.9±8.5 | 25.8±8.8 | 0.146 | 22.9±8.1 | 25.2±9.3 | 0.406 |
| AST in U/L | 21.3±4.0 | 23.2±3.4 | 0.102 | 21.4±2.1 | 23.0±4.5 | 0.116 |
| ALP in U/L | 70.6±18.5 | 75 (61, 86) | 0.297 | 68.0±13.0 | 74.5±19.4 | 0.220 |
| γ-GGT in U/L | 17 (13.0, 28.8) | 19 (14, 24) | 0.772 | 18.5 (14.0, 23.3) | 17 (14, 25) | 0.826 |
| ALB in g/L | 47.2±2.3 | 47.2 (46.2, 48.5) | 0.746 | 47.7±1.9 | 47.7 (44.9, 48.5) | 0.372 |
| GLB in g/L | 30.2±3.1 | 28.7±3.1 | 0.132 | 28.4±2.8 | 29.9±3.3 | 0.121 |
| LSM in kPa | 6.2±1.3 | 6.5±1.4 | 0.436 | 5.0±0.52 | 6.9 (6.4, 8.0) <0.001 |
| HBV DNA in lg IU/mL | 2.72±0.40 | 4.11 (3.75, 4.44) <0.001 | 3.52 (2.48, 3.86) | 4.11 (3.75, 4.44) | 0.203 |
| HBeAg, negative: positive | 18: 0 | 22: 2 | 0.498 | 18: 0 | 22: 2 | 0.498 |

Data with a normal distribution are expressed as mean±SD, and data not normally distributed are represented as medians (P_{25}, P_{75}). CHB, chronic hepatitis B; HBV, hepatitis B virus; LSM, liver stiffness measurement; TB, total bilirubin; DB, direct bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; γ-GGT, gamma-glutamyl transferase; ALB, albumin; GLB, globulin; HBeAg, hepatitis B e antigen.
Table 3. Effectiveness assessment after 4 weeks treatment

<table>
<thead>
<tr>
<th></th>
<th>Low viral load (20 ≤ HBV DNA &lt; 2,000 IU/mL)</th>
<th>High viral load (HBV DNA &gt; 2,000 IU/mL)</th>
<th>p value</th>
<th>Low stiffness (LSM &lt; 6.0 kPa)</th>
<th>High stiffness (6.0 kPa ≤ LSM &lt; 9.0 kPa)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVR in %, n/N</td>
<td>12/13, 92.3%</td>
<td>15/22, 68.2%</td>
<td>0.210</td>
<td>12/14, 85.7%</td>
<td>15/21, 71.4%</td>
<td>0.431</td>
</tr>
<tr>
<td>HBV DNA decrease in lg IU/mL</td>
<td>1.36±0.43</td>
<td>2.79±0.71</td>
<td>&lt;0.001</td>
<td>2.13±0.93</td>
<td>2.34±0.95</td>
<td>0.518</td>
</tr>
<tr>
<td>TB in μmol/L</td>
<td>11.7 (10.7, 18.1)</td>
<td>13.2 (11.5, 15.5)</td>
<td>0.775</td>
<td>12.7 (11.1, 14.7)</td>
<td>13.3 (11.1, 18.1)</td>
<td>0.434</td>
</tr>
<tr>
<td>DB in μmol/L</td>
<td>4.7 (4.1, 7.0)</td>
<td>5.4 (4.3, 6.2)</td>
<td>0.987</td>
<td>4.8 (4.3, 5.7)</td>
<td>5.7 (4.1, 7.0)</td>
<td>0.516</td>
</tr>
<tr>
<td>ALT in U/L</td>
<td>19 (13.5, 28.0)</td>
<td>24 (15.8, 31.5)</td>
<td>0.533</td>
<td>22.0±8.8</td>
<td>23.6±10.6</td>
<td>0.639</td>
</tr>
<tr>
<td>AST in U/L</td>
<td>19.0 (16.5, 25.5)</td>
<td>22 (18.5, 25.0)</td>
<td>0.511</td>
<td>19.0 (16.8, 23.3)</td>
<td>22.0 (18.0, 25.5)</td>
<td>0.154</td>
</tr>
<tr>
<td>ALP in U/L</td>
<td>72.5±17.7</td>
<td>74.5±12.9</td>
<td>0.701</td>
<td>76 (62.8, 80.8)</td>
<td>72.0 (66.0, 81.0)</td>
<td>0.907</td>
</tr>
<tr>
<td>γ-GT in U/L</td>
<td>16.0 (12.5, 39.5)</td>
<td>17.5 (14.0, 24.8)</td>
<td>0.987</td>
<td>17.0 (14.0, 25.3)</td>
<td>17.0 (13.5, 27.0)</td>
<td>0.987</td>
</tr>
<tr>
<td>ALB in g/L</td>
<td>45.9±2.0</td>
<td>46.6±2.2</td>
<td>0.361</td>
<td>46.9±1.9</td>
<td>46.0±2.2</td>
<td>0.219</td>
</tr>
<tr>
<td>GLB in g/L</td>
<td>29.1±2.1</td>
<td>28.4±2.2</td>
<td>0.319</td>
<td>27.7±1.8</td>
<td>29.1±2.4</td>
<td>0.070</td>
</tr>
</tbody>
</table>

*When HBV DNA is unmeasurable, take the lowest limit (20 IU/mL) and calculate. Data with normal distribution are expressed as mean±SD, and data not normally distributed are represented as medians (P25, P75). CVR, complete virological response.

Fig. 3. Effectiveness of TAF for CHB patients with different viral loads. n.s. means that the difference is not statistically significant and the p value is more than 0.5. TAF, tenofovir alafenamide; CHB, chronic hepatitis B; HBV, hepatitis B virus.

Fig. 4. Effectiveness of TAF for CHB patients with different LSM. n.s. means that the difference is not statistically significant and the p value is more than 0.5. TAF, tenofovir alafenamide; CHB, chronic hepatitis B; LSM, liver stiffness measurement; HBV, hepatitis B virus.
viral load over 10^8 IU/mL did not obtain CRV, and his HBV DNA went down to 10^3 IU/mL after 48 weeks of treatment. Thus, more data are needed on the effectiveness of TAF for patients in the immune-tolerant phase.

**Positive interventions in immune control phase patients are encouraged**

Secondly, we also observed the effectiveness of TAF in CHB patients in the immune control phase (also known as having inactive HBsAg carrier status). According to the Chinese guidelines, the characteristics of these patients are as follows: (1) serological marker HBsAg <1×10^3 IU/mL, anti-HBs-negative, HBeAg-negative, anti-HBe-positive and anti-HBc positive; (2) HBV DNA <2×10^3 IU/mL; (3) ALT normal; and (4) no or only mild (liver) inflammation, and there may be varying degrees of fibrosis. At present, there is controversy over whether or not to initiate antiviral therapy for such patients. Some scholars do not recommend starting antiviral therapy for these patients, mainly due to two concerns. One is that hepatic histological progression is sluggish in those patients, and therefore antiviral effect will not be good for these patients. Another concern regards the long-time effectiveness and safety of the current first-line oral antiviral agents, such as entecavir and tenofovir disoproxil fumarate (TDF), are potent the current first-line oral antiviral agents. For example, although the current first-line oral antiviral agents, such as entecavir and tenofovir disoproxil fumarate (TDF), are potent on Diagnosing Fibrosis Based on Transient Elastography (2018 Update), different degrees of liver stiffness would affect the decision of antiviral treatment in clinic. For normal-ALT CHB patients with LSM ≥9.0 kPa, it is recommended to initiate antiviral therapy directly and monitor complications of liver cirrhosis or HCC. When LSM is between 6.0–9.0 kPa, it is considered to perform liver biopsy to evaluate disease status and then initiate individualized antiviral treatment based on disease status. When LSM <6.0 kPa, liver stiffness should be monitored regularly and antiviral treatment should be individualized.

Therefore, we set up low (LSM <6.0 kPa) and high (6.0 ≤LSM <9.0 kPa) LSM groups. None of the patients in either group was eligible for antiviral indications by the 2019 Chinese guideline and by the 2018 expert consensus above. Our results showed that CHB patients in both groups had a detection limit <HBV DNA <2,000 IU/mL, indicating that antiviral treatment should be individualized.

**LSM: possibly an overestimated index within antiviral indications**

In addition, we investigated whether or not LSM would affect antiviral effectiveness. Generally, transient elastography is used as a kind of noninvasive ultrasonic technology to assess liver stiffness. According to the Expert Consensus on Diagnosing Fibrosis Based on Transient Elastography Technology (2018 Update), different degrees of liver stiffness would affect the decision of antiviral treatment in clinic. For normal-ALT CHB patients with LSM ≥9.0 kPa, it is recommended to initiate antiviral therapy directly and monitor complications of liver cirrhosis or HCC. When LSM is between 6.0–9.0 kPa, it is considered to perform liver biopsy to evaluate disease status and then initiate individualized antiviral treatment based on disease status. When LSM <6.0 kPa, liver stiffness should be monitored regularly and antiviral treatment should be individualized.

Therefore, we set up low (LSM <6.0 kPa) and high (6.0 ≤LSM <9.0 kPa) LSM groups. None of the patients in either group was eligible for antiviral indications by the 2019 Chinese guideline and by the 2018 expert consensus above. Our results showed that CHB patients in both groups had a significant response to TAF antiviral therapy. Moreover, the efficacy of the low LSM group seemed to be higher; the undetectable rate of HBV DNA in the high LSM group was lower.

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**Table 4. Antiviral indications from different regions guidelines for patients with HBeAg negativity and normal ALT**

<table>
<thead>
<tr>
<th>Patients with HBeAg negativity and normal ALT</th>
<th>HBV DNA &gt;2,000 IU/mL</th>
<th>Detection limit &lt;HBV DNA &lt;2,000 IU/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>AASLD (2018)</td>
<td>Monitor ALT and HBV DNA every 3 months for the first year, then every 6 months</td>
<td>Do not treat; monitor ALT and HBV DNA levels every 3-6 months and HBsAg annually</td>
</tr>
<tr>
<td>EASL (2017)</td>
<td>1) Liver biopsy or noninvasive tests indicate at least moderate fibrosis; 2) Patients with family history of HCC or cirrhosis and extrahepatic manifestations can be treated even without typical treatment indications</td>
<td>Patients with family history of HCC or cirrhosis and extrahepatic manifestations can be treated even without typical treatment indications</td>
</tr>
<tr>
<td>APASL (2015)</td>
<td>Treat if moderate to severe inflammation or significant fibrosis indicated by noninvasive tests or liver biopsy</td>
<td>Same as left</td>
</tr>
<tr>
<td>In China (2019)</td>
<td>1) Liver biopsy results of G2 and/or S2 stage or above; 2) Older age than 30 years, with a family history of liver cirrhosis or cancer; 3) Older age than 30 years, and the noninvasive diagnosis technique or liver biopsy suggested obvious liver inflammation or fibrosis; 4) HBV-related extrahepatic manifestations</td>
<td>Same as left</td>
</tr>
</tbody>
</table>

AASLD, American Association for the Study of Liver Diseases; EASL, European Association for the Study of the Liver; APASL, Asia Pacific Society of Hepatology.
than that in the low one at each time point, but there was no statistical significance. This may suggest that even for CHB patients whose LSM is below 9.0 kPa, antiviral therapy can be unhesitatingly initiated without liver biopsy evidence, as long as their HBV DNA is detectable. More broadly speaking, for normal-ALT CHB patients with detectable HBV DNA, antiviral treatment could be initiated regardless of liver stiffness, which will be good news for patients in certain conditions where liver biopsy or liver stiffness testing is not available.

The cost effectiveness of antiviral treatment

Although long-term antiviral therapy for all patients with normal ALT and HBV DNA positivity costs more per month, seemingly it has less economic cost in terms of long-term benefits and has significant benefits in disease control. In a South Korea cost-effectiveness analysis, it was found that long-term nucleos(t)ide analog therapy for patients with untreated minimally active CHB may contribute positively toward individual clinical benefit and the national health care budget.28 Similarly, compared with delaying treatment until progression to active hepatitis phase in CHB patients, starting antiviral therapy in the immune-tolerant phase is more cost-effective, decreasing drug costs and affecting producing antiviral therapy in the immune-tolerant phase is more cost-effective.

In a South Korea cost-effectiveness analysis, it was found that long-term nucleos(t)ide analog therapy for patients with untreated minimally active CHB may contribute positively toward individual clinical benefit and the national health care budget.28 Similarly, compared with delaying treatment until progression to active hepatitis phase in CHB patients, starting antiviral therapy in the immune-tolerant phase is more cost-effective, decreasing drug costs and affecting producing antiviral therapy in the immune-tolerant phase is more cost-effective.28 Similarly, compared with delaying treatment until progression to active hepatitis phase in CHB patients, starting antiviral therapy in the immune-tolerant phase is more cost-effective, decreasing drug costs and affecting producing antiviral therapy in the immune-tolerant phase is more cost-effective.

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The authors have no conflict of interest related to this publication.

Author contributions

Design of the research (JY, FD), acquisition of data (YC, YYS, WKG, YA, XQY), analysis and interpretation of data (WKG, YC), drafting of the manuscript (WKG), and critical revision of the manuscript for important intellectual content (JY, FD). All authors read and approved the final version of the manuscript.

Data sharing statement

The data used to support the findings of this study are available from the corresponding author upon reasonable request.

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