ABSTRACT
Background: The purpose was to compare the efficacy between tenofovir disoproxil fumarate (TDF) and lamivudine (LMV) in children with nucleos(t)ide-naive chronic hepatitis B (CHB) infection. Patients with CHB were treated with TDF in the immune-reactive phase and compared with a historical control group of patients treated with LMV before the TDF era.

Methods: Hepatitis B virus (HBV) DNA titer decrements (> 3 log10 IU/mL) were monitored after treatment initiation. The treatment duration for HBV DNA clearance (< 357 IU/mL) and complete response (HBeAg loss and HBV DNA clearance) were analyzed. The follow-up period was 96 weeks.

Results: Sixteen patients were treated with TDF and compared with a historical control group of 24 patients treated with LMV. HBV DNA decrement (> 3 log10 IU/mL) was achieved in 100% (16/16) of the TDF group but in only 62.5% (15/24) of the LMV group (P = 0.005) at 48 weeks. The HBV DNA clearance (< 357 IU/mL) in the TDF and LMV groups was, respectively, as follows: 62.5% (10/16) and 25.0% (6/24) at 12 weeks (P = 0.018), 81.3% (13/16) and 37.5% (9/24) at 24 weeks (P = 0.006), 93.8% (15/16) and 50.0% (12/24) at 48 weeks (P = 0.004), and 100% (16/16) and 54.2% (13/24) at 96 weeks (P = 0.001). Complete response occurred in 41.7% (5/12) of HBeAg-positive patients in the TDF group and 28.6% (6/21) of the LMV group at 96 weeks (P = 0.443).

Conclusion: TDF monotherapy for 96 weeks produced a significantly more effective virologic response than LMV monotherapy in children with nucleos(t)ide-naive CHB.

Keywords: Tenofovir; Lamivudine; Chronic Hepatitis B; Children

INTRODUCTION
In East Asia, hepatitis B virus (HBV) infection is endemic and its transmission occurs mainly via the perinatal mode during infancy and early childhood.1,2 Unlike horizontal infection during adulthood, vertical transmission progresses to chronic hepatitis B (CHB) infection in about 80%–90% of cases.1 Furthermore, HBV proliferation and liver damage remain sustained for many years. The cumulative percentage of children converting to the immune-reactive phase was reported to be 39.7% among patients aged < 18 years and 11.7% among those aged < 12 years.3 Therefore, continuous regular follow-up is necessary to ensure proper treatment and to minimize necro-inflammation and sequelae during the immune-active...
phase.\textsuperscript{1,4} Long-term lamivudine (LMV) treatment in children has significantly improved the seroconversion rate of HBeAg and HBsAg than interferon-alpha in children with genotype C; however, antiviral resistance occurs in 27.5% by 96 weeks of follow-up.\textsuperscript{5,6}

Newly developed nucleos(t)ide analogues are currently being used, and these are known to have stronger antiviral activity and lower frequency of viral resistance during long-term use than previous drugs. Currently, entecavir (ETV) or tenofovir disoproxil fumarate (TDF) is the first-choice treatment in adults.\textsuperscript{7-9} In a randomized, placebo-controlled trial of adolescents with human immunodeficiency virus infection, TDF was effective in normalizing alanine aminotransferase (ALT) levels and suppressing HBV DNA, and was well tolerated not only by treatment-naive patients but also those with treatment experience.\textsuperscript{10}

Nevertheless, TDF was not allowed in children younger than 12 years until now, and a 96 weeks' comparison of the efficacy of TDF and LMV has not been conducted yet in children. The aim of this study was to compare the therapeutic efficacy of TDF with that of LMV in children and adolescents with nucleos(t)ide-naive CHB, among whom genotype C is predominant.

**METHODS**

**Baseline characteristics of patients**

This retrospective cohort study involved four centers (Department of Pediatrics of Kyungpook National University Children's Hospital, Kyungpook National University Hospital, Seoul National University Children's Hospital, and Seoul National University Bundang Hospital) in Korea. Nucleos(t)ide-naive patients with CHB treated with TDF (TDF group) were sequentially enrolled from January 2013 to September 2016, when confirmed to be in the immune-reactive phase. The TDF group was compared with a historical control group of patients treated with LMV (LMV group) at Kyungpook National University Hospital from January 2005 to December 2009 (when TDF was not available for children).

Inclusion criteria (all of the listed criteria are mandatory):

1) Age > 8 but < 18 years.
2) HBeAg-positive or HBeAg-negative hepatitis in the immune-reactive phase.
3) Pretreatment HBV DNA level > 10^6 IU/mL.
4) Immune-reactive phase, defined as pretreatment ALT levels more than two times the upper limit of the normal value persisting for
   i. > 6 months
   ii. or > 3 months without HBV DNA decrease
   iii. or regardless of the period of elevated ALT level if the pathology revealed necro-inflammatory changes and/or fibrotic changes of more than grade 2 and stage 2 according to the Knodell histological activity index.
5) Refusal of patients to be enrolled in a concurrent global TDF trial (age 2–12 years)

Exclusion criteria:

1) Previous treatment with antiviral agents.
2) Treatment with corticosteroids, cytotoxic agents, or immunosuppressive drugs within the last 6 months.
3) Co-infection with other viruses such as cytomegalovirus, human immunodeficiency virus, Epstein-Barr virus, or hepatitis C virus.
4) Comorbidities with other liver diseases such as immune or metabolic disorders, or steatohepatitis.
5) Present enrollment in a TDF clinical trial (age 2–12 years).

**Treatment protocol**
The TDF group was compared with the historical control group (LMV group treated before TDF became available for children). TDF was given orally once daily at a dose of 8 mg/kg (maximal dose 300 mg, tablet). LMV was orally administered once daily at a dose of 3 mg/kg (maximal dose 100 mg, tablet or syrup). During all follow-up periods, adverse events were checked by using laboratory data and clinical assessments.

**Monitoring**
The duration of HBV DNA clearance (< 357 IU/mL) and titer decrements (≥ 3 log₁₀ IU/mL), ALT normalization (< 40 U/L), and HBeAg loss were monitored after the initiation of each treatment and compared between groups. The detection limit for the HBV DNA assay was 20 IU/mL from 2009, whereas it was 357 IU/mL before 2009. The proportion of inadequate responders (> 2,000 IU/mL) was also compared at 24 weeks of treatment. The aspartate aminotransferase/ALT titers were monitored before and 4 weeks after the start of treatment, and follow-up measurements were conducted at intervals of 8–12 weeks. During the follow-up periods, serum HBsAg, anti-HBs, HBeAg, and anti-HBe levels were assessed by using a commercially available electrochemiluminescence immunoassay method (ARCHITECT PLUS; Abbott, Lake Bluff, IL, USA). The HBV DNA level was monitored by using real-time polymerase chain reaction (PCR) (Exicycler™ 96; BIONEER, Daejeon, Korea; detection limit 20 IU/mL).

**Definition of response**
Virologic response was defined as an undetectable HBV DNA level as determined with real-time PCR assay (< 357 IU/mL). Virologic breakthrough was defined as a confirmed increase in HBV DNA level of > 1 log₁₀ IU/mL in comparison with the nadir (lowest value) HBV DNA level during treatment. Complete response was defined as the combination of HBeAg loss, HBV DNA clearance, and normalization of the ALT level after the start of treatment.

**Statistical analysis**
Data were analyzed by using χ² test or Fisher’s exact test to examine the significance of the association between categorical variables. Independent t-tests or Welch’s t-tests were performed for the comparison of continuous variables such as age, HBV DNA values, and pretreatment ALT.

All statistical analyses were performed with statistical software (Statistical Package for the Social Sciences, version 18; SPSS Inc., Chicago, IL, USA). A P value of < 0.05 was defined as statistically significant.

**Ethics statement**
Written informed consent was obtained from the TDF group, but not obtained from the LMV historical control group. The study protocol was reviewed and approved by Institutional Review Boards of Kyungpook National University Medical Center (IRB file No. 2016-12-025) and Seoul National University Hospital (IRB file No. 1608-032-783).
RESULTS

Baseline characteristics
Sixteen patients (male:female, 6:10; age range, 10.1–17.5 years; mean ± standard deviation [SD], 14.1 ± 2.1) were enrolled for TDF treatment. The historical control group was composed of 24 patients (male:female, 14:10; age range, 8.0–15.2 years; mean ± SD, 12.5 ± 1.9) treated with LMV at Kyungpook National University Hospital from January 2005 to December 2009 before the TDF era.

The baseline demographics of the subjects are shown in Table 1. Except for age, there was no statistically significant difference between the groups in HBV DNA values, pretreatment ALT, or sex. The mean pretreatment HBV DNA level of four HBeAg-negative patients in the TDF group was 7.4 ± 0.5 log_{10} IU/mL (range, 6.6–7.8 log_{10} IU/mL), which was not statistically different from the mean level in HBeAg-positive patients in the TDF group (7.3 ± 0.7 log_{10} IU/mL; range, 6.1–8.2 log_{10} IU/mL; P = 0.777). The mean (± SD) age at treatment was 14.1 ± 2.1 years in the TDF group and 12.5 ± 1.9 years in the LMV group (P = 0.020). All 16 patients in the TDF group and 24 patients in the LMV group were followed for 96 weeks.

ALT level
The mean pretreatment ALT level was 224 ± 161.2 U/L (range, 81–619 U/L) in the TDF group, whereas the mean level was 178.3 ± 118.6 U/L (range, 81–597 U/L) in the LMV group. The pretreatment ALT levels of biopsy-proven patients were all > 80 U/L.

By week 24, the proportion of all patients who had normal ALT levels was 93.8% (15/16) in the TDF group and 95.8% (23/24) in the LMV group (P = 0.767). ALT normalization (< 40 U/L) was achieved in both the TDF and LMV groups: 93.8% (15/16) and 100% (24/24) at 48 weeks (P = 0.215), and 100% (16/16) and 62.5% (15/24) at 96 weeks (P = 0.007) (Fig. 1).

Antiviral potency of TDF compared with LMV
HBV DNA clearance (HBV DNA level < 357 IU/mL)
The HBV DNA clearance (< 357 IU/mL) in the TDF and LMV groups, respectively, was as follows: 62.5% (10/16) and 25.0% (6/24) at 12 weeks (P = 0.018), 81.3% (13/16) and 37.5% (9/24) at 24 weeks (P = 0.006), 93.8% (15/16) and 50.0% (12/24) at 48 weeks (P = 0.004), and 100% (16/16) and 54.2% (13/24) at 96 weeks (P = 0.002) (Fig. 1).

Mean duration for HBV DNA clearance
The mean duration for HBV DNA clearance (time interval between treatment initiation and HBV DNA becoming < 357 IU/mL) was 22.5 ± 18.0 weeks in all 16 patients (100%) of the TDF

| Table 1. Baseline demographics of the TDF- and LMV-treated CHB groups |
|-----------------|-----------------|-----------------|
| Parameters      | TDF (n = 16)    | LMV (n = 24)    | P value |
| Sex (male:female) | 6:10           | 14:10           |        |
| Age, median ± SD (range) | 14.1 ± 2.1 (10.1–17.5) | 12.9 ± 1.9 (8.0–15.2) | 0.020  |
| Pretreatment ALT, U/L | 224.0 ± 161.2  | 178.3 ± 118.6   | 0.307  |
| Pretreatment HBV DNA, log_{10} IU/mL |              |                  |        |
| ≥ 8             | 7.3 ± 0.6      | 7.1 ± 0.2       | 0.420  |
| ≥ 6 and < 8     | 2 (12.5)       | 0 (0)           |        |
| HBeAg-positive:HBeAg-negative CHB | 12:4 | 21:3 |        |

Values are presented as number of patients (%) or mean ± SD not otherwise specified.
TDF = tenofovir disoproxil fumarate, LMV = lamivudine, CHB = chronic hepatitis B, SD = standard deviation, ALT = alanine aminotransferase, HBV = hepatitis B virus.
group; however, it was 27.7 ± 19.8 weeks in only 54.2% (13/24) of the LMV group ($P$ = 0.467).

In the comparison of 16 HBeAg-positive and HBeAg-negative patients of the TDF group and 21 HBeAg-positive patients of the LMV group, the mean duration for HBV DNA clearance was 22.5 ± 18.0 weeks in 100% (16/16) of the TDF group and 30.5 ± 20.3 weeks in 52.4% (11/21) of the LMV group ($P$ [duration/proportion] = 1.000/0.036) (Table 2). Among HBeAg-positive patients, the mean duration for HBV DNA clearance was 26.0 ± 19.7 weeks in 100% (12/12) of the TDF group and 30.5 ± 20.3 weeks in 52.4% (11/21) of the LMV group ($P$ [duration/proportion] = 0.592/0.004) (Table 3).

**Mean duration for HBV DNA titer decrement > 3 log$_{10}$ IU/mL**

The mean duration for HBV DNA titer decrement ($> 3$ log$_{10}$ IU/mL) was 15.0 ± 9.3 weeks in all 16 patients (100%) of the TDF group; however, it was 14.5 ± 5.0 weeks in 79.2% (19/24) of the LMV group ($P$ = 0.857). HBV DNA decrement ($> 3$ log$_{10}$ IU/mL) was achieved in 100% (16/16) of the TDF group and in 52.4% (11/21) of the LMV group ($P$ [duration/proportion] = 0.592/0.004) (Table 3).

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**Table 2.** Duration of treatment and proportion of patients for HBV DNA decrement among HBeAg-positive and HBeAg-negative patients with CHB

| HBV DNA decrement | TDF (n = 16) | LMV (n = 21) | $P$ (duration) | $P$ (proportion) |
|-------------------|--------------|--------------|----------------|------------------|
| $> 3$ log$_{10}$ IU/mL | Mean duration ± SD | 15.0 ± 9.3 wk | 15.0 ± 5.4 wk | 1.000 | 0.036 |
| No. (%) | 16 (100) | 16 (76.2) |
| HBV DNA < 357 IU | Mean duration ± SD | 22.5 ± 18.0 wk | 30.5 ± 20.3 wk | 0.290 | 0.001 |
| No. (%) | 16 (100) | 11 (52.4) |

HBV = hepatitis B virus, CHB = chronic hepatitis B, TDF = tenofovir disoproxil fumarate, LMV = lamivudine, SD = standard deviation.

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**Table 3.** Duration of treatment and proportion of patients for HBV DNA decrement and HBeAg negativization, among HBeAg-positive patients with CHB

| HBV DNA decrement | TDF (n = 12) | LMV (n = 21) | $P$ (duration) | $P$ (proportion) |
|-------------------|--------------|--------------|----------------|------------------|
| $> 3$ log$_{10}$ IU/mL | Mean duration ± SD | 16.0 ± 10.7 wk | 15.0 ± 5.4 wk | 0.770 | 0.067 |
| No. (%) | 12 (100) | 16 (76.2) |
| HBV DNA < 357 IU | Mean duration ± SD | 26.0 ± 19.7 wk | 30.5 ± 20.3 wk | 0.592 | 0.004 |
| No. (%) | 12 (100) | 11 (52.4) |
| HBeAg negativization | Mean duration ± SD | 11.6 ± 8.4 wk | 28.0 ± 23.1 wk | 0.210 | 0.443 |
| No. (%) | 5 (41.7) | 6 (28.6) |

HBV = hepatitis B virus, CHB = chronic hepatitis B, TDF = tenofovir disoproxil fumarate, LMV = lamivudine, SD = standard deviation.
of patients in the TDF group, but in only 62.5% (15/24) of patients in the LMV group at 48 weeks after the initiation of treatment \( (P = 0.005) \). In the comparison of 16 HBeAg-positive and HBeAg-negative patients of the TDF group and 21 HBeAg-positive patients of the LMV group, the mean duration for HBV DNA titer decrement \( (> 3 \log_{10} \text{IU/mL}) \) was 15.0 \( \pm \) 9.3 weeks in 100% (16/16) of the TDF group and 15.0 \( \pm \) 5.4 weeks in 76.2% (16/21) of the LMV group \( (P [\text{duration/proportion}] = 1.000/0.036) \) (Table 2). Among HBeAg-positive patients, the mean duration for HBV DNA titer decrement \( (> 3 \log_{10} \text{IU/mL}) \) was 16.0 \( \pm \) 10.7 weeks in 100% (12/12) of the TDF group and 15.0 \( \pm \) 5.4 weeks in 76.2% (16/21) of the LMV group \( (P [\text{duration/proportion}] = 1.000/0.036) \) (Table 2).

Inadequate virologic suppression and partial virologic response
Inadequate virologic suppression \( (> 2,000 \text{IU/mL}) \) at 24 weeks' follow-up was noted in 12.5% (2/16) of the TDF group and 54.2% (13/24) of the LMV group \( (P = 0.008) \). Partial virologic response \( (357–2,000 \text{IU/mL}) \) was observed in 6.3% (1/16) and 12.5% (3/24) of patients at 24 weeks \( (P = 0.519) \).

Virologic breakthrough
Among patients treated with TDF, there was no evidence of breakthrough over the course of the study. On the other hand, one patient (4.2%) in the LMV group experienced virologic breakthrough.

Serology
Among patients who were HBeAg positive at baseline, 12.5% (2/12) in the TDF group and 23.8% (5/21) in the LMV group achieved complete response (HBeAg loss and HBV DNA < 357 IU/mL) by week 48 \( (P = 0.629) \), and 41.7% (5/12) of the TDF group and 28.6% (6/21) of the LMV group achieved complete response by week 96 \( (P = 0.443) \) (Fig. 1). Only one child showed HBsAg loss in the LMV group at 43 months after treatment; however, no patient achieved HBsAg and anti-HBs seroconversion until the last follow-up after 96 weeks. Among HBeAg-positive patients, the mean duration of HBeAg negativization was 11.6 \( \pm \) 8.4 weeks in 41.7% (5/12) of the TDF group and 28.0 \( \pm \) 23.1 weeks in 28.6% (6/21) of the LMV group \( (P [\text{duration/proportion}] = 0.210/0.443) \) (Table 3).

Adverse events
There was no adverse event related to treatment during the study period in the TDF group; however, one patient in the LMV group had peripheral neuropathy. Decrement of bone mineral density was not monitored through bone densitometry (dual-energy X-ray absorptiometry scan).

Antiviral resistance and long-term follow-up monitoring
Cumulative antiviral resistance occurred in 33.3% (8/24) and 41.7% (10/24) in the LMV group at 96 and 144 weeks of follow-up, respectively. Their treatment was switched to another option including tenofovir rescue therapy.

Until 192 weeks of treatment start, 8 of 24 patients had achieved complete response and 13 of 24 patients had confirmed mutations in the LMV group. Furthermore, the treatment protocol was changed, such as adding adefovir (or tenofovir) or switching to ETV (+/- adefovir or tenofovir), in 15 patients. In the TDF group, there was no viral mutation until up to 192 weeks of follow-up.
DISCUSSION

This is the first study to evaluate the effectiveness of TDF among children, including those aged < 12 years, with CHB in real-life clinical practice. Although there are data on the effectiveness of TDF over placebo from a randomized clinical trial in adolescents with CHB, there is currently no relevant data concerning children < 12 years old and no comparison data with the old treatment protocol with LMV. Our study revealed that TDF monotherapy was more effective than LMV monotherapy (historical control) in children with CHB.

In the era of newly developed nucleos(t)ide analogues, TDF and ETV are the first-choice treatment for CHB in adults because of their long-term efficacy and safety. The Food and Drug Administration has approved ETV for children > 2 years old in 2012 and TDF for children > 12 years old in 2015. However, the therapeutic potency and long-term efficacy of TDF compared with LMV have not been previously studied in children.

In the aspect of suppression of HBV DNA, the results of this study were relatively better than those of previous adult studies on TDF. In this study, the proportion of virologic responses was 81.3%, 93.8%, and 100% at 24, 48, and 96 weeks, whereas adult studies reported a virologic response rate of 22.8%–49% at 24 weeks, 71.5%–92% at 48 weeks, and 96% at 96 weeks. The proportion of viral suppression (> 3 log₁₀ IU/mL) was better with TDF than with LMV, among HBeAg-positive and HBeAg-negative patients with CHB.

Our results confirmed that the antiviral efficacy of TDF in children correspond to what has been observed in adults. The rate of complete response was 12.5% (2/12) at 48 weeks and 41.7% (5/12) at 96 weeks after treatment. The reported results from adult studies in Korea and that in Western countries are similar. Kim et al. reported that 15.2% achieved an absence of serum HBV DNA and detection of anti-HBe after 12 months of TDF treatment among nucleos(t)ide-naive patients with genotype C CHB. On the other hand, other Korean adult studies reported 3.8% and 9.8% rates of HBeAg loss or seroconversion to anti-HBe at 12 months. Marcellin et al. demonstrated a rate of HBeAg seroconversion of 21% at week 48. Idilman et al. reported that the cumulative probability of HBeAg loss increased from 16.8% at 1 year to 27.6% at 2 years of TDF therapy. In other long-term studies, HBeAg loss was observed in 34%–45% and HBeAg seroconversion was observed in 25% at 3 years.

Long-term treatment with LMV is effective in the aspects of HBV DNA clearance, HBeAg seroconversion rate, and ALT normalization in children, and is capable of achieving HBsAg seroconversion in toddlers. However, the use of LMV has been restricted by its propensity to lead to the development of treatment-resistant viral mutations. Treatment-resistant mutations were reported in 10%–19% of children treated with LMV for 1 year and in 23%–69.4% after 2 years.

In the aspect of insurance coverage, ETV and TDF has been allowed in Korean children since 2015; thus, some strategies were applied for LMV-resistant children between 2012 and 2015. Although TDF is now available for children > 12 years old, LMV is still considered effective for children < 6 years of age in Korea where genotype C is predominant. A global study on the efficacy and safety of TDF in children between 2 and 11 years old is ongoing.

Despite concerns on adherence to treatment among children and adolescents, no viral breakthrough developed in the TDF group in this study. All cases of virologic breakthrough
were related to nonadherence to TDF dosage in an adult study,\textsuperscript{27} with evidence of no phenotypic or genotypic drug resistance at 144 weeks of follow-up of TDF monotherapy.\textsuperscript{28}

The one patient who did not achieve ALT normalization was thought to have nonalcoholic fatty liver disease because of persistent central obesity during the treatment period. TDF therapy for patients with CHB in Asian countries showed no significant difference compared with studies in Western countries where genotypes A and D prevail.\textsuperscript{19,29-31} Although genotypes were not identified in this study, genotype C is nearly 100\% prevalent in Korea, where vertical or perinatal infection is the main transmission route.\textsuperscript{32,33} However, the results of this study imply that the therapeutic effect of TDF in children is excellent independent of the genotype.\textsuperscript{34}

This study has some limitations. The first limitation is the relatively small number of patients included. However, these patients could represent the national data because of the extremely low HBV prevalence in Korean children. Selection bias could be present because concurrent enrollment into a TDF phase 3 study was ongoing during this study period, although phase 3 trial participants were not enrolled in this study. Second, the enrolled patients in the TDF group were older than those of the LMV group, and age could negatively affect the therapeutic efficacy of TDF.\textsuperscript{3} However, despite these limitations, the outcomes in the TDF group were better than those in the LMV group. Nevertheless, this is the first study to evaluate the efficacy of TDF in real-life clinical practice among children with CHB.

In conclusion, TDF therapy in nucleos(t)ide-naive children and adolescents was highly effective for antiviral suppression compared with LMV in real-life clinical practice. No resistance to TDF was observed through 96 weeks. TDF has a higher genotypic barrier to resistance than LMV for children with genotype C.

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REFERENCES

1. Choe BH. The epidemiology and present status of chronic hepatitis B in Korean children. Korean J Pediatr 2008;51(7):696-703.
2. Choe HJ, Choe BH. What physicians should know about the management of chronic hepatitis B in children: east side story. World J Gastroenterol 2014;20(13):3582-9.
3. Hong SJ, Park HJ, Chu MA, Choi BS, Choe BH. The rate of conversion from immune-tolerant phase to early immune-clearance phase in children with chronic hepatitis B virus infection. Pediatr Gastroenterol Hepatol Nutr 2014;17(1):41-6.
4. Jonas MM, Block JM, Haber BA, Karpen SJ, London WT, Murray KF, et al. Treatment of children with chronic hepatitis B virus infection in the United States: patient selection and therapeutic options. Hepatology 2010;52(6):2192-205.
5. Choe BH, Lee JH, Jang YM, Jang CH, Oh KW, Kwon S, et al. Long-term therapeutic efficacy of lamivudine compared with interferon-alpha in children with chronic hepatitis B: the younger the better. J Pediatr Gastroenterol Nutr 2007;44(1):92-8.

6. Kim JM, Choe BH, Chu MA, Cho SM. Comparison of lamivudine-induced HBsAg loss rate according to age in children with chronic hepatitis B. Korean J Hepatol 2009;15(2):168-78.

7. Liaw YF, Kao JH, Piratvisuth T, Chan HL, Chien RN, Liu CJ, et al. Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2012 update. Hepatol Int 2012;6(3):531-61.

8. Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. Hepatology 2009;50(3):664-2.

9. European Association for the Study of the Liver. EASL clinical practice guidelines: management of chronic hepatitis B virus infection. J Hepatol 2012;57(1):167-85.

10. Murray KF, Szenborn L, Wysocki J, Rossi S, Corsa AC, Dinh P, et al. Randomized, placebo-controlled trial of tenofovir disoproxil fumarate in adolescents with chronic hepatitis B. Hepatology 2012;56(6):2018-26.

11. Chang TT, Lai CL, Yoon SK, Lee SS, Coelho HS, Carrilho FJ, et al. Entecavir treatment for up to 5 years in patients with hepatitis B e antigen-negative chronic hepatitis B. Hepatology 2010;51(2):422-30.

12. Chang TT, Liaw YF, Wu SS, Schiff E, Han KH, Lai CL, et al. Long-term entecavir therapy results in the reversal of fibrosis/cirrhosis and continued histological improvement in patients with chronic hepatitis B. Hepatology 2010;52(3):886-93.

13. Gordon SC, Krastev Z, Horban A, Petersen J, Sperl J, Dinh P, et al. Efficacy of tenofovir disoproxil fumarate at 240 weeks in patients with chronic hepatitis B with high baseline viral load. Hepatology 2013;58(2):505-13.

14. Jonas MM, Chang MH, Sokal E, Schwarz KB, Kelly D, Kim KM, et al. Randomized, controlled trial of entecavir versus placebo in children with hepatitis B envelope antigen-positive chronic hepatitis B. Hepatology 2016;63(2):377-87.

15. Ahn SS, Chon YE, Kim BK, Kim SU, Kim DY, Ahn SH, et al. Tenofovir disoproxil fumarate monotherapy for nucleos(t)ide-naive chronic hepatitis B patients in Korea: data from the clinical practice setting in a single-center cohort. Clin Mol Hepatol 2014;20(3):261-6.

16. Marcellin P, Heathcote EL, Buti M, Gane E, de Man RA, Krastev Z, et al. Tenofovir disoproxil fumarate versus adefovir dipivoxil for chronic hepatitis B. N Engl J Med 2008;359(23):2442-55.

17. Marcellin P, Zoulim F, Hézode C, Causse X, Roche B, Truchi R, et al. Effectiveness and safety of tenofovir disoproxil fumarate in chronic hepatitis B: a 3-year, prospective, real-world study in France. Dig Dis Sci 2016;61(10):3072-83.

18. Woo G, Tomlinson G, Nishikawa Y, Kowgier M, Sherman M, Wong DK, et al. Tenofovir and entecavir are the most effective antiviral agents for chronic hepatitis B: a systematic review and Bayesian meta-analyses. Gastroenterology 2010;139(4):1218-29.

19. Kim JH, Jung SW, Byun SS, Shin JW, Park BR, Kim MH, et al. Efficacy and safety of tenofovir in nucleos(t)ide-naive patients with genotype C chronic hepatitis B in real-life practice. Int J Clin Pharm 2015;37(6):1228-34.

20. Jung SK, Kim KA, Ha SY, Lee HK, Kim YD, Lee BH, et al. Tenofovir disoproxil fumarate monotherapy for nucleos(t)ide analogue-naive and nucleos(t)ide analogue-experienced chronic hepatitis B patients. Clin Mol Hepatol 2015;21(1):41-8.

21. Idilman R, Gunsar F, Koruk M, Keskini O, Meral CE, Gulsen M, et al. Long-term entecavir or tenofovir disoproxil fumarate therapy in treatment-naive chronic hepatitis B patients in the real-world setting. J Viral Hepat 2015;22(5):504-10.
22. Heathcote EJ, Marcellin P, Buti M, Gane E, De Man RA, Krastev Z, et al. Three-year efficacy and safety of tenofovir disoproxil fumarate treatment for chronic hepatitis B. *Gastroenterology* 2011;140(1):132-43.

23. Ozgenc F, Arikan C, Sertoz RY, Nart D, Aydogdu S, Yagci RV. Effect of long-term lamivudine in chronic hepatitis B virus-infected children. *Antivir Ther* 2004;9(5):729-32.

24. Sokal EM, Kelly DA, Mizerski J, Badia JA, Arcias JA, Schwarz KB, et al. Long-term lamivudine therapy for children with HBeAg-positive chronic hepatitis B. *Hepatology* 2006;43(2):225-32.

25. Hong SJ, Kim YH, Choe BH, Park HI, Tak WY, Kweon YO. Current role of lamivudine regarding therapeutic response and resistance in children with chronic hepatitis B. *Pediatr Gastroenterol Hepatol Nutr* 2013;16(2):80-8.

26. Feld JJ, Heathcote EJ. Hepatitis B e antigen-positive chronic hepatitis B: natural history and treatment. *Semin Liver Dis* 2006;26(2):116-29.

27. Kitrinos KM, Corsa A, Liu Y, Flaherty J, Snow-Lampart A, Marcellin P, et al. No detectable resistance to tenofovir disoproxil fumarate after 6 years of therapy in patients with chronic hepatitis B. *Hepatology* 2014;59(2):434-42.

28. Snow-Lampart A, Chappell B, Curtis M, Zhu Y, Myrick F, Schwalder J, et al. No resistance to tenofovir disoproxil fumarate detected after up to 144 weeks of therapy in patients monoinfected with chronic hepatitis B virus. *Hepatology* 2011;53(3):763-73.

29. Ha NB, Trinh HN, Rosenblatt L, Nghiem D, Nguyen MH. Treatment outcomes with first-line therapies with entecavir and tenofovir in treatment-naive chronic hepatitis B patients in a routine clinical practice. *J Clin Gastroenterol* 2016;50(2):169-74.

30. Pan CQ, Chan S, Trinh H, Yao A, Bae H, Lou L. Similar efficacy and safety of tenofovir in Asians and non-Asians with chronic hepatitis B. *World J Gastroenterol* 2015;21(18):5524-31.

31. Tsai NC, Marcellin P, Buti M, Washington MK, Lee SS, Chan S, et al. Viral suppression and cirrhosis regression with tenofovir disoproxil fumarate in Asians with chronic hepatitis B. *Dig Dis Sci* 2015;60(1):260-8.

32. Kim H, Jee YM, Song BC, Shin JW, Yang SH, Mun HS, et al. Molecular epidemiology of hepatitis B virus (HBV) genotypes and serotypes in patients with chronic HBV infection in Korea. *Intervirology* 2007;50(1):52-7.

33. Song BC, Cui XJ, Kim H. Hepatitis B virus genotypes in Korea: an endemic area of hepatitis B virus infection. *Intervirology* 2005;48(2-3):133-7.

34. Marcellin P, Ahn SH, Ma X, Caruntu FA, Tak WY, Elkashab M, et al. Combination of tenofovir disoproxil fumarate and peginterferon α-2a increases loss of hepatitis B surface antigen in patients with chronic hepatitis B. *Gastroenterology* 2016;150(1):134-44.e10.