Chronic hepatitis B (CHB) is a major health problem in the world. CHB affects 350–400 million people worldwide.\(^1\) Seventy percent of patients with chronic hepatitis and liver cirrhosis, and 65%–75% of patients with hepatocellular carcinoma were related with positive serum hepatitis B surface antigen (HBsAg).\(^2,3\) Annually, one million people die from liver cirrhosis, hepatic failure, and hepatocellular carcinoma.\(^1\)

The goals of treatment of CHB are to prevent liver complications and to improve survival rate.\(^4,5\) The ultimate goal is to achieve HBsAg loss and seroconversion, but because covalently closed circular DNA persists in the nucleus despite treatment, complete clearance of HBV is almost impossible.\(^6\) Undetectable HBV DNA, alanine aminotransferase (ALT) normalization, hepatitis B surface antigen (HBeAg) loss or seroconversion, and histologic improvement are used to estimate the response of treatment in clinical practice.\(^6,7\)

Current guidelines recommend a single agent with a potent antiviral activity and high genetic barrier, such as tenofovir (TDF) or entecavir (ETV), as the first-line antiviral agents for CHB.\(^6,7\) Both TDF and ETV selectively inhibit HBV viral replication with potent activity.\(^8,9\) ETV is effective as monotherapy in treatment-naïve patients with low rates of resistance (0.5%–1.2%) for up to 6 years of treatment.\(^10,11\) Significant resistance mutations to TDF have not been reported in patients with HBV monoinfection.\(^12,13\) However, there are few studies that directly compare their effectiveness.

We compared antiviral response and safety of TDF and ETV for achieving complete virologic response (CVR) in
treatment-naïve CHB patients. We also evaluated the rates of normalization of ALT and HBeAg loss or seroconversion, and predictive factors for CVR.

**PATIENTS AND METHODS**

**Patients**

The study enrolled 18-70 year old patients with HBeAg-positive or HBeAg-negative chronic HBV who had never received any prior treatment. CHB patients with an HBV DNA level of ≥2,000 IU/mL and ALT level of two times or more than the upper normal limit were included. Patients with compensated liver cirrhosis were included if the DNA level was ≥2,000 IU/mL, regardless of the ALT level. Liver cirrhosis was diagnosed through imaging studies such as computed tomography and/or magnetic resonance imaging and/or abdominal sonography, and/or proven esophageal or gastric varix by esophagastroduodenoscopy, and/or low platelet count (less than 100,000/μL). All patients were treated with TDF or ETV monotherapy for at least 6 months. Further eligibility criteria were no evidence of decompensated liver cirrhosis and no evidence of co-infection with hepatitis C virus, other hepatitis viruses, or human immunodeficiency virus. Patients with poor compliance, other malignant disease except hepatocellular carcinoma, other causes of liver cirrhosis except HBV infection, follow up loss in clinics, or a history of any chemotherapies, any radiation therapies, or any immunosuppressive therapies were excluded.

We performed a retrospective cohort study of adult CHB patients who visited the hepatology clinic at our Hospital from September 2010 to April 2014. TDF group consisted of consecutive patients treated with TDF 300 mg daily since December 2012, and the ETV group consisted of patients treated with ETV 0.5 mg daily since September 2010. Although most patients of the ETV group were treated for more than 12 months, only up to 12 months of their data were used for comparison of effectiveness between the TDF group and the ETV group.

Patients were identified through electronic search of all CHB patient medical records at our treatment center, and data were retrieved via individual record review. This study was approved by the Institutional Review Board of the Konkuk University Medical Center (KUH1010592).

**Study design**

The primary objective was to evaluate virologic response of TDF and ETV at 3, 6, 9, and 12 months, measured by the proportion of patients achieving CVR defined as undetectable serum HBV DNA (<120 copies/mL).[^6][^7] Virologic breakthrough was defined as two consecutive 1 log₁₀ or > 10-fold increase in plasma HBV DNA from nadir or two consecutive values ≥120 copies/mL after being CVR. High viral load was defined as serum HBV DNA ≥ 7 log₁₀ copies/mL.

The secondary outcomes were the changes in HBV DNA level and ALT level, normalization of ALT level (≤40 IU/mL), the overall incidence of HBeAg loss or seroconversion to antibody to HBeAg in the HBeAg-positive patients, as well as HBsAg loss. All adverse effects were investigated on the basis of medical records of all patients. Adverse effects of TDF and ETV and discontinuation of the drugs due to adverse effects were evaluated by review of the medical records for symptoms and laboratory data. Renal toxicity was defined as increase in creatinine level of ≥0.3 mg/dL or 1.5 times above baseline, or serum phosphorus level <2 mg/dL.[^10] Hepatotoxicity was defined as elevation of ALT level more than two times above baseline or more than 10 times the upper normal limit, or total bilirubin more than 1.5 times the upper normal limit.[^15]

**Statistical analysis**

All statistical data were analyzed using SPSS Inc. for Windows, ver. 17.0. Categorical variables were analyzed using the Chi-square test. Continuous variables were evaluated using the Student’s t test. The Kaplan–Meier survival analysis was used to estimate the proportion of CVR and normalization of ALT level. The Cox regression analysis was used to estimate predictors of CVR. For all statistical tests, a two-sided P value of < 0.05 was considered significant.

**RESULTS**

**Patients’ characteristics**

A total of 107 patients were eligible as per inclusion criteria, of whom 49 were treated with TDF and 58 were treated with ETV. Baseline characteristics were similar between the TDF and the ETV groups [Table 1]. Of the total cohort, 55 patients were male, the mean age was 50.3 years, 53 patients (49.5%) had liver cirrhosis, and 62 patients (57.9%) were HBeAg positive. The mean of HBV DNA level was 7.01 log₁₀ copies/mL. HBeAg was positive in 53.1% of the TDF group and 62.1% of the ETV group, respectively. The mean of baseline HBV DNA in each group was 6.98 log₁₀ copies/mL in the TDF group and 7.05 log₁₀ copies/mL in the ETV group. The follow-up duration was significantly different between the two groups, the TDF group was 8.45 months and the ETV group was 18.7 months (P <0.001). The ETV group had greater number of patients with liver cirrhosis than the TDF group (60.3% vs. 36.7%, P = 0.015).

**Treatment responses**

The estimated proportion of CVR between the TDF and the ETV group was 6.1% vs. 13.8% at 3 months, 44.9% vs. 39.7% at 6 months, 53.4% vs. 62.3% at 9 months and 89.6% vs. 85.2% at 12 months, respectively [Figure 1].
There was no significant difference in CVR rates between the TDF and the ETV groups ($P = 0.991$). The decline of HBV DNA level was $-4.83 \log_{10}$ copies/mL from 6.98 log$_{10}$ copies/mL to 2.15 log$_{10}$ copies/mL in the TDF group, and $-4.84 \log_{10}$ copies/mL from 7.05 log$_{10}$ copies/mL to 2.21 log$_{10}$ copies/mL in the ETV group [Figure 2]. Changes of HBV DNA levels between the TDF and the ETV group were not different ($P = 0.809$). Virologic breakthrough was not observed in the two groups during the 12 months of treatment.

We analyzed the virologic response of TDF and ETV in patients with high viral load (HBV DNA $\geq 7 \log_{10}$ copies/mL). The estimated proportion of CVR between the TDF and the ETV group was 21.4% vs. 26.7% at 6 months, 30.2% vs. 46.0% at 9 months, and 80.0% vs. 73.0% at 12 months, respectively [Figure 3]. There was no significant difference in CVR rates between the TDF and the ETV groups ($P = 0.669$).

The rates of HBeAg loss and seroconversion to anti-HBe among the HBeAg-positive patients were not significantly different between the TDF and the ETV groups [Table 2]. One patient (3.8%) in the TDF group and two patients (5.6%) in the ETV group experienced HBeAg loss, and two patients (5.6%) in the ETV group experienced seroconversion to anti-HBe antibody. No patient experienced HBsAg loss in the two groups.

There were 39 patients with abnormal ALT at the baseline in the TDF group and 43 patients in the ETV group. At 12 months, 31 (79.5%) patients achieved ALT normalization in the TDF group and 39 (90.1%) in the ETV group. There was no difference in changes of ALT level between the TDF and the ETV groups ($P = 0.862$) [Figure 4].

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**Table 1: Baseline characteristics of treatment-naïve chronic hepatitis B patients treated with TDF or ETV**

|                                | Total  | TDF (n=49) | ETV (n=58) | $P$  |
|--------------------------------|--------|------------|------------|------|
| Age (year)                     | (n=107) | 50.4 (11.7)| 51.7 (10.3)| 0.205|
| Gender                         | (SD)   | 22 (44.9%) | 33 (56.9%) | 0.216|
| Male                           |        | 55 (51.4%) | 36 (75.8%) |       |
| Female                         |        | 52 (48.6%) | 23 (25%)   |       |
| History of alcohol             |        | 26 (24.3%) | 14 (24.1%) | 0.966|
| History of smoking             |        | 9 (8.4%)   | 6 (10.3%)  | 0.433|
| Family history of HBV          |        | 44 (41.1%) | 22 (37.9%) | 0.466|
| Family history of HCC          |        | 12 (11.2%) | 5 (8.6%)   | 0.355|
| Hypertension                   |        | 14 (13.1%) | 9 (15.5%)  | 0.417|
| Diabetes mellitus              |        | 8 (7.5%)   | 4 (6.9%)   | 0.804|
| Liver cirrhosis                |        | 53 (49.5%) | 35 (60.3%) | 0.015|
| Hepatocellular carcinoma       |        | 12 (11.2%) | 8 (13.8%)  | 0.358|
| HBeAg positive                 |        | 62 (57.9%) | 36 (62.1%) | 0.466|
| HBV DNA (log$_{10}$ copies/mL)|        | 7.01 (1.43)| 7.05 (1.33)| 0.809|
| Mean (SD)                      | (log$_{10}$ copies/mL) | 7.01 (1.43) | 7.05 (1.33) | 0.809|
| High viral load                |        | 58 (54.2%) | 30 (51.7%) | 0.575|
| ALT (IU/L)                     |        | 190 (337)  | 165 (351)  | 0.394|
| Mean (SD)                      | (IU/L)  | 169.4 (62.5)| 185.4 (8.1)| 0.886|
| eGFR (mL/min/1.73m$^2$)        |        | 85.5 (7.7) | 85.4 (8.1) |       |
| Platelets (K/µL)               |        | 169.4 (62.5)| 185.4 (8.1)| 0.886|
| Creatinine (mg/dL)             |        | 0.79 (0.17)| 0.80 (0.18)| 0.619|
| Follow-up time (months)        |        | 13.9 (8.7) | 18.6 (9.3) | <0.001|

TDF: Tenofovir, ETV: Entecavir, SD: Standard deviation, HBV: Hepatitis B virus, HCC: Hepatocellular carcinoma, HBeAg: Hepatitis B e antigen, ALT: Alanine aminotransferase, eGFR: Estimated glomerular filtration rate.

*Comparison of the TDF group vs. the ETV group.

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**Figure 1:** Proportion of patients achieving complete virologic response between the TDF and the ETV groups. TDF, tenofovir; ETV, entecavir

**Figure 2:** Changes in HBV DNA level between the TDF and the ETV groups. TDF, tenofovir; ETV, entecavir
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There were significant adverse events. One patient (2.0%) in the TDF group and one patient (1.7%) in the ETV group experienced adverse renal effects \( (P = 0.904) \). Three patients (6.1%) in the TDF group and two patients (3.4%) in the ETV groups experienced hepatic adverse effect \( (P = 0.514) \). No significant differences were observed between the TDF and the ETV groups in the overall incidence of all adverse effects. And there were no discontinuations or dose modifications due to adverse effects.

**Predictors of virologic response**

The Cox regression univariate analysis for predictors showed that gender, HBeAg-positivity, and baseline HBV DNA level were significantly associated with CVR at 12 months of TDF or ETV treatment. However, presence of liver cirrhosis in TDF vs. ETV was not a significant factor for CVR. Multivariate analysis showed only the baseline HBV DNA level as a significant predictor of CVR (hazard ratio = 0.797; 95% confidence interval = 0.676–0.940; \( P = 0.007 \)).

**DISCUSSION**

In this study, we investigated antiviral response and safety of TDF and ETV in treatment-naïve CHB patients. Both TDF and ETV had good virologic responses that were comparable between the groups. TDF and ETV have a similar mechanism to inhibit HBV DNA polymerase. TDF is an analog of adenosine 5’-monophosphate that inhibits HBV DNA polymerases by direct binding,[12] and ETV is a carboxylic analog of 2’-deoxyguanosine that inhibits HBV DNA polymerase by competing with the natural deoxyguanosine triphosphate.[16] Rates of CVR for TDF range from 67% to 90% and ETV from 74% to 91% after 12 months of treatment, respectively.[17] The current guidelines recommend TDF and ETV as first-line antiviral agents for CHB because of potent viral suppression activity and low rates or absence of resistance.[6,7,10-13]

There were no significant differences in baseline characteristics analysis of gender, HBeAg status, and baseline HBV DNA level between the TDF and the ETV groups. However, follow-up time of the TDF group was shorter than the ETV group, because TDF was recently (end of 2012) approved for the treatment of CHB patients, in Korea. The prevalence of liver cirrhosis was higher in the ETV group, in our study. This might be due to extension of insurance coverage for ETV use in CHB patients with liver cirrhosis, during the study period.

Our results showed no significant difference in CVR rates between the TDF and the ETV group \( (P = 0.991) \), and no difference in changes of HBV DNA level between the two groups \( (P = 0.809) \). There are few studies comparing the efficacy between TDF and ETV. Previous studies reported no significant difference in CVR rates between TDF and ETV in nucleos (t) ide-naive patients after 48 weeks of treatment.[18,19] A recent meta-analysis study suggested that there was no significant difference in virologic response between TDF and ETV in CHB patients after 24 weeks and
48 weeks of antiviral therapy. However, the comparative efficacy between TDF and ETV, particularly in patients with high viral load, remains controversial. A recent study reported that TDF had better virologic response than ETV in CHB patients after 24 months of treatment; however, there was no difference in the decline in serum HBV DNA levels.

The rates of HBeAg loss and seroconversion to anti-HBe were not significantly different among the HBeAg-positive patients, between the TDF and the ETV groups. Nevertheless, HBeAg loss rates and seroconversion rates were lower than those in the previous studies. Most Korean CHB patients are infected with HBV genotype C via maternal transmission at birth. This genotype is known to have a lower rate of HBeAg seroconversion, a more rapid progress to hepatocelluar carcinoma and cirrhosis, and have a higher rate of relapse after antiviral treatments, compared with other genotypes.

ALT normalization is usually used as a virologic response and indication of cessation of liver injury. We found no significant difference in biochemical response between the TDF and the ETV groups (P =0.065). ALT normalization rates of the TDF group (79.5%) and the ETV group (90.1%) were similar to previous reports.

The safety profile was not different between the TDF and the ETV groups [Table 3]. There were no deaths, discontinuations, or dose modifications due to serious adverse effects. All adverse effects were well tolerated by patients, during TDF or ETV therapy. TDF and ETV are known to have few adverse effects that are more tolerable than interferon or other antiviral agents. However, ETV is classified as a category C drug that has potential risks for the fetus, and should be restricted during the first trimester of pregnancy; and since the serious adverse effect of TDF is nephrotoxicity, all TDF-treated patients should be investigated for their creatinine clearance during therapy. Although there were no serious adverse effects in our study, the study duration of 12 months was not enough to observe long-term adverse effects.

On the basis of the Cox regression analysis, high HBV DNA level at baseline was a significant negative predictor of virologic response. A recent study suggested that TDF was superior to ETV for achieving CVR in HBeAg-positive CHB patients with high HBV DNA levels, defined as a baseline HBV DNA >6 log10 IU/mL. On the other hand, our results suggested that there was no significant difference in CVR rates between TDF and ETV in patients with high viral load [Figure 4]. Some earlier studies supported our results. However, additional monitoring is needed to investigate long-term virologic response and virologic breakthrough during long-term use of TDF or ETV, in patients with high HBV DNA level.

This study included a cohort of ETV- or TDF-treated CHB patients and compared the efficacy and safety at 12 months of treatment. Limitations of our study were short follow-up times of the TDF group, relatively small size, as well as the retrospective design. Nevertheless, our study was significant because there are few comparative studies of virologic response and safety between TDF and ETV in treatment-naïve CHB patients.

### CONCLUSION

Our results suggested that both TDF and ETV effectively maintain CVR, and are safe and well tolerated in treatment-naïve CHB patients. Furthermore, high HBV DNA level at baseline is a negative predictive factor for achieving CVR. Additional research on long-term data and virologic response in patients with high viral load are needed.

### REFERENCES

1. Dienstag JL. Hepatitis B virus infection. N Engl J Med 2008;359:1486-500.
2. Chae HB, Kim JH, Kim JK, Yim HJ. Current status of liver diseases in Korea: Hepatitis B. Korean J Hepatol 2009;15:S13-24.
3. Kim SR, Kudo M, Hino O, Han KH, Chung YH, Lee HS; Organizing Committee of Japan-Korea Liver Symposium. Epidemiology of

### Table 3: The Cox regression analysis for predictive factors for complete virologic response

| Factors          | Univariate | Multivariate |
|------------------|------------|--------------|
|                  | HR         | CI (95%)     | P      | HR           | CI (95%)     | P    |
| Age              | 1.018      | 0.998-1.039 | 0.085 | 0.984        | 0.962-1.006 | 0.158|
| Sex (male)       | 1.922      | 1.216-3.036 | 0.005 | 1.466        | 0.895-2.399 | 0.128|
| Liver cirrhosis  | 0.793      | 0.502-1.252 | 0.319 |             |              |      |
| TDF vs. ETV      | 1.002      | 0.630-1.594 | 0.992 |             |              |      |
| Baseline HBV DNA | 0.713      | 0.607-0.836 | <0.001| 0.797        | 0.676-0.940 | 0.007|
| Baseline ALT     | 1.000      | 0.999-1.001 | 0.680 |             |              |      |
| HBeAg positive   | 2.335      | 1.468-3.715 | <0.001| 0.893        | 0.513-1.554 | 0.689|

HR: Hazard ratio, CI: Confidence interval, TDF: Tenofovir, ETV: Entecavir, HBV: Hepatitis B virus, ALT: Alanine aminotransferase, HBeAg: Hepatitis B e antigen.
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1. Lampertico P. Partial virological response to nucleos(t)ide analogues in naïve patients with chronic hepatitis B: From guidelines to field practice. J Hepatol 2009;50:644-7.
2. Dogan UB, Kara B, Gumurdulu Y, Soylu A, Akin MS. Comparison of the efficacy of tenofovir and entecavir for the treatment of nucleos (t) ide-naïve patients with chronic hepatitis B. Turk J Gastroenterol 2012;23:247-52.
3. Guzelbulut F, Ovunc AO, Oetinkaya ZA, Senates E, Gökden Y, Saltürk AG, al et. Comparison of the efficacy of entecavir and tenofovir in chronic hepatitis B. Hepatogastroenterology 2012;59:477-80.
4. Ke W, Liu L, Zhang C, Ye X, Gao Y, Zou S, et al. Comparison of efficacy and safety of Tenofovir and entecavir in chronic hepatitis B virus infection: A systematic review and meta-analysis. PLoS One 2014;9:e98865.
5. Ceylan B, Yardimci C, Fincanci M, Eren G, Tozalgan U, Muderrisoglu C, et al. Comparison of tenofovir and entecavir in patients with chronic HBV infection. Eur Rev Med Pharmacol Sci 2013;17:2467-73.
6. Bae SH, Yoon SK, Jang JW, Kim CW, Nam SW, Choi JY, et al. Hepatitis B virus genotype C prevails among chronic carriers of the virus in Korea. J Korean Med Sci 2005;20:816-20.
7. 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;50:52-7.
8. Lee JM, Ahn SH, Chang HY, Shin JE, Kim DY, Sim MK, et al. Reappraisal of HBV genotypes and clinical significance in Koreans using MALDI-TOF mass spectrometry. Korean J Hepatol 2004;10:260-70.
9. Fontana RJ. Side effects of long-term oral antiviral therapy for hepatitis B. Hepatology 2009;49:S185-95.
10. Heathcore EJ, Marcellin P, Buti M. Three-year efficacy and safety through 4 years of tenofovir disoproxil fumarate treatment for chronic hepatitis B. Gastroenterology 2011;140:132-43.
11. Gao L, Trinh HN, Li J, Nguyen MH. Tenofovir is superior to entecavir for achieving complete viral suppression in HBsAg-positive chronic hepatitis B patients with high HBV DNA. Aliment Pharmacol Ther 2014;39:629-37.
12. 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;58:505-13.

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