Telbivudine therapy for chronic hepatitis B: A journey to identify super-responders and to optimize treatment using the roadmap model

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Abstract
Hepatitis B virus (HBV) infection is one of the most serious health problems worldwide with a high risk for cirrhosis and liver cancer. Several antiviral agents have been approved for the treatment of chronic hepatitis B, leading to a rapid reduction in HBV DNA and normalization of serum alanine aminotransferase levels. Telbivudine, a potent inhibitor of HBV replication, has been shown to be well tolerated. Because of the emergence of drug resistance, optimization strategies for telbivudine therapy have been shown to improve patient responses. Optimal baseline characteristics in so-called super-responders have been used to predict the virological response. Baseline HBV DNA levels < 9 log10 copies/mL (2 × 109 IU/mL) or alanine aminotransferase levels of more than or equal to twofold the upper limit of normal in HBeAg-positive patients and HBV DNA < 7 log10 copies/mL (2 × 108 IU/mL) in HBeAg-negative patients were strong predictors for virological response. In addition, the roadmap model, based on early virological response at week 24 of therapy, is considered as a powerful tool to identify patients at risk of treatment failure (HBV DNA ≥ 300 copies/mL, i.e. 60 IU/mL) and to reduce the risk of antiviral resistance. When considering pre-treatment characteristics and on-treatment responses, telbivudine may provide physicians with a wide choice of options to effectively treat patients with chronic hepatitis B, especially those with or at risk of renal impairment, or women of childbearing age.

Introduction
Hepatitis B virus (HBV) infection is among the most common persistent viral infections in humans. In 2010, over 248 million individuals worldwide were estimated to have chronic hepatitis B (CHB), with a wide variation in the prevalence of hepatitis B surface antigen (HBsAg) among countries. The primary treatment goals for patients with CHB are to increase survival and to prevent progression of the disease, which can manifest as cirrhosis, liver failure, or hepatocellular carcinoma (HCC). Risk factors for progression of CHB include persistently elevated levels of HBV DNA and alanine aminotransferase (ALT), male sex, older age, family history of HCC, and elevated alpha-fetoprotein. Some viral factors may lead to poor clinical outcomes. The REVEAL study showed a strong correlation between HBV replication and progression to cirrhosis, with a serum HBV DNA level ≥ 10 000 copies/mL (2000 IU/mL) as a strong predictor of HCC. Furthermore, patients with HBV genotypes C and D have a higher risk of cirrhosis and HCC. HBV mutant strains, including the HBV precore nucleotide 1896 stop codon mutation, basal core promoter A1762T/G1764A variants, and the deletion mutations within the pre-S gene are significantly associated with progressive liver cell damage. HBsAg quantification has been recently proposed as a tool to monitor patients. High serum HBsAg level was shown to be the strongest predictor of HCC occurrence in patients with a low viral load.

Several antiviral agents have been approved for the treatment of CHB. The first nucleos(t)ide analog (NA) was lamivudine, followed by clevudine, emtricitabine, entecavir, and telbivudine; two other NAs, adefovir and tenofovir, became available in recent years. These NAs have different antiviral potencies and drug-resistance patterns. Entecavir and tenofovir are considered the...
two most potent NAs with a high genetic barrier to resistance development.\textsuperscript{10} The main goals of NAs are to suppress viral replication and reduce the risk of disease progression to cirrhosis or HCC.\textsuperscript{12} NAs lead to a rapid reduction in HBV DNA and normalization of serum ALT levels.\textsuperscript{13} However, most patients require prolonged or even lifelong therapy for sustained viral suppression.\textsuperscript{14} The treatment duration of NAs remains unclear. Discontinuation of NA therapy is possible for hepatitis B e antigen (HBeAg)-positive patients if they achieve HBeAg seroconversion and maintain undetectable HBV DNA.\textsuperscript{15,16} For HBeAg-negative patients, discontinuation of NAs is an option if appropriate stopping criteria are met.\textsuperscript{17}

Telbivudine is also a potent inhibitor of HBV replication and has been shown to be generally well tolerated.\textsuperscript{18} Because of the emergence of drug resistance, optimization strategies for telbivudine therapy have been shown to improve patient responses.\textsuperscript{19,20} Early virological response at week 24 of therapy has been shown to be a good predictor of better clinical outcomes.\textsuperscript{21} Optimization therapy according to baseline characteristics, such as gender, duration of infection, HBeAg level, HBV DNA level, and ALT level, has been used as a strategy to predict the virological response to NAs.\textsuperscript{16,22} Nevertheless, to date, few studies have assessed predictors of response to NAs.\textsuperscript{23–25} Patients with optimal baseline characteristics (so-called super-responders) are more likely to achieve favorable outcomes after treatment with telbivudine.\textsuperscript{26} The identification of predictors of clinical outcomes is important to increase the chance of treatment success, decrease the risk of resistance, and help define the appropriate treatment duration for HBeAg-positive patients. In this review, we outline the general efficacy and safety of telbivudine, provide a brief overview of the rationale for the roadmap model, and discuss how this model can be utilized in patients with CHB in order to optimize telbivudine therapy.

### Treatment response to telbivudine in patients with chronic HBV infection

#### General efficacy of telbivudine.

Telbivudine, a potent antiviral, is an orally administered synthetic thymidine nucleoside analog with specific activity against HBV.\textsuperscript{18,27} The general efficacy of telbivudine (ability to reduce HBV DNA and ALT levels and stimulate HBeAg seroconversion) has been discussed extensively in literature reviews and meta-analyses.\textsuperscript{28–30} A more recent network meta-analysis demonstrated the superiority of telbivudine over adefovir, entecavir, and lamivudine in HBeAg seroconversion or HBeAg loss.\textsuperscript{31} Although the short-term efficacy of telbivudine with regard to the rate of undetectable HBV DNA level appears to be comparable with entecavir, the results showed improved suppression of HBV DNA with long-term telbivudine treatment in comparison with adefovir and lamivudine.\textsuperscript{31} In a 2-year, multinational, randomized, phase 3 trial (GLOBE), telbivudine provided effective treatment of patients with CHB compared with lamivudine.\textsuperscript{32} The rate of undetectable viremia (<300 copies/mL, i.e., 60 IU/mL) was significantly higher with telbivudine (55.6%) than with lamivudine (38.5%) in HBeAg-positive patients. Higher rates were also observed in HBeAg-negative patients (82.0% vs 56.7%, respectively). After two additional years of treatment, telbivudine continued to provide effective viral suppression (76.2% in HBeAg-positive patients and 86.0% in HBeAg-negative patients).

As emergence of viral resistance is an important concern with prolonged telbivudine treatment, early virological response at week 24 of therapy has been used as a strategy to reduce the risk of resistance.

#### Super-responders to telbivudine treatment.

Low HBV DNA levels and high ALT levels prior to NA therapy are considered to be predictors of HBeAg seroconversion.\textsuperscript{16,25,33} In the GLOBE study, on-treatment monitoring was evaluated in 1367 patients with CHB.\textsuperscript{32} Logistic regression analyses showed that baseline serum HBV DNA level was a significant independent predictor of better clinical outcomes at 2 years of treatment with telbivudine.\textsuperscript{32} Other multivariate logistic regression analyses showed that serum HBV DNA levels <9 log\textsubscript{10} copies/mL or ALT levels of more than or equal to twofold the upper limit of normal (ULN) at baseline were strong predictors for virological response in HBeAg-positive patients.\textsuperscript{26} The proportion of patients with undetectable HBV DNA at 2 years was higher in this subgroup (77.3%) than in all HBeAg-positive patients (55.6%). The results were similar for HBeAg-negative patients with baseline HBV DNA <7 log\textsubscript{10} copies/mL (2×ULN) (89.2% vs 82.0%) (Table 1). The high rates of undetectable HBV DNA after 2 years of telbivudine treatment were associated with lower telbivudine resistance (3.1% vs 10.8%, respectively).\textsuperscript{26} In a different study, there was a significant difference in HBeAg seroconversion between super-responder patients (83.3%) and all patients receiving telbivudine (46.4%).\textsuperscript{34} Although in this study the 2-year cumulative resistance to telbivudine was relatively high (21.7%), this rate decreased to 13.5% in super-responder patients. The association of these baseline predictors with improved outcomes was further enhanced by adding treatment response at week 24 to the algorithm. In a real-world study, super-responder patients had satisfactory virological, biochemical, and serological responses after 2 years of treatment with telbivudine. HBeAg-positive patients achieved favorable serological responses, and better virological responses were shown in both HBeAg-positive and HBeAg-negative patients (78.6% and 96.6%, respectively) (Table 1).\textsuperscript{35} In another study, when combining the baseline characteristics of ALT >2×ULN with on-treatment responses at week 24, telbivudine compared with entecavir showed significantly higher rates of HBeAg seroconversion (57.1% vs 41.7%, respectively) and ALT normalization (100% vs 66.7%, respectively) at week 48.\textsuperscript{36} The combination used (baseline ALT and HBV DNA level at week 24) in this study led to a low rate of telbivudine resistance (6.7%). Patients without genotypic resistance after 2 years of treatment with telbivudine maintained effective viral suppression and ALT normalization after two additional years of telbivudine treatment (Table 1).\textsuperscript{37} The results from a prospective trial (EFFORT) using the roadmap model showed that telbivudine significantly improved efficacy outcomes at 2 years.\textsuperscript{20} This study showed that among patients with HBV DNA levels <9 log\textsubscript{10} copies/mL (2×10\textsuperscript{8} IU/mL) or ALT levels ≥2×ULN, the rates of HBV DNA <300 copies/mL (60 IU/mL) was significantly higher in the telbivudine plus adefovir group than in the telbivudine monotherapy group (90.9% vs 75.9%, P<0.001, respectively) at 5 years of treatment.\textsuperscript{38} ALT normalization rates
### Table 1  Baseline predictors for telbivudine treatment response

| References | Study design/patients | Favorable predictors | Clinical outcomes |
|------------|-----------------------|----------------------|-------------------|
| Tsai et al. [34] | Retrospective, comparative study versus entecavir/CHB patients with virological resistance $n=230$ | HBeAg-positive patients: Baseline HBV DNA <10^9 copies/mL (2x10^8 IU/mL), ALT ≥2xULN and undetectable HBV DNA at week 24 | HBeAg seroconversion (telbivudine versus entecavir): 46.4% versus 42.9% in all patients and 83.3% versus 41.2% at year 2 ($P=0.008$) in super-responders. Resistance rate with telbivudine at year 2 in all patients: 21.7%. This rate decreased from 21.7% to 11.8% and 13.5% at year 2 after applying super-responders (optimal baseline characteristics) and roadmap concept (undetectable HBV DNA at week 24), respectively. |
| Wang et al. [35] | Prospective, open-label, multicenter study/CHB patients $n=116$ | HBeAg-positive patients: Baseline serum HBV DNA ≤9 log_{10} copies/mL (2x10^8 IU/mL), ALT ≥2xULN and 24-week PCR negativity | ALT normalization at week 104: 64.3% Seroconversion at week 104: 50% PCR negativity at week 104: 78.6% Resistance was observed in 1 patient |
| Tsai et al. [36] | Prospective study/CHB patients $n=195$ | HBeAg-negative patients: HBV DNA ≤7 log_{10} copies/mL (2x10^6 IU/mL) and 24-week PCR negativity | HBeAg-positive CHB patients: ALT normalization at week 48: 100% with telbivudine and 67% with entecavir Seroconversion at week 48: 57% versus 42%, respectively PCR negativity at week 48: 86% versus 100%, respectively Resistance rate: 0% in both groups HBeAg-negative CHB patients: ALT normalization at 48 weeks: 79% versus 65%, respectively PCR negativity at week 48: 93% versus 100%, respectively Resistance rate: 3.43% versus 0%, respectively |
| Wang et al. [37] | Open-label extension study from GLOBE/015 studies/CHB patients $n=502$ | HBeAg-positive patients: Baseline serum HBV DNA <9 log_{10} copies/mL (2x10^8 IU/mL), ALT ≥2xULN and 24-week PCR negativity | ALT normalization at week 208: 90.0% PCR negativity at week 208: 93.3% Resistance was observed in 2 patients |
| Zeuzem et al. [36] | Prospective, randomized, double-blind, phase 3 study/CHB patients $n=680$ | HBeAg-positive patients: Baseline serum HBV DNA ≤9 log_{10} copies/mL (2x10^8 IU/mL), ALT ≥2xULN | Comparison of patients with baseline predictors to overall population at 2 years: Serum HBV DNA negative: 77.3% versus 55.6%, respectively HBeAg seroconversion: 47.1% versus 29.6%, respectively ALT normalization: 75% versus 69.5%, respectively Resistance rate: 11.3% versus 25.1%, respectively |
| Fan et al. [39] | Retrospective study/HBeAg-positive CHB patients $n=606$ | Favorable group: Baseline anti-HBc ≥4.4 log_{10} IU/mL and baseline HBV DNA <9 log_{10} copies/mL (2x10^8 IU/mL) | HBeAg seroconversion: 37.1% versus 14.5% in the favorable and unfavorable groups, respectively |
Telbivudine therapy for chronic hepatitis B

J-H Kao et al.

Table 1. (Continued)

| References | Study design/patients | Favorable predictors | Clinical outcomes |
|------------|-----------------------|----------------------|-------------------|
| Sun et al. 20 | Prospective, randomized, open-label, controlled, multicenter study/CHB patients | ALT, alanine aminotransferase; CHB, chronic hepatitis B; DNA, deoxyribonucleic acid; HBc, hepatitis B core antibody; HBV, hepatitis B virus; PCR, polymerase chain reaction; ULN, upper limit of normal. | Increase from 37.1% to 48.6% in the favorable group when combined with on-treatment response at week 24.

Unfavorable group: Baseline anti-HBc ≥ 4.4 log10 IU/mL and baseline HBV DNA > 300 copies/mL (60 IU/mL).

Telbivudine therapy plus adefovir was added to patients with suboptimal early virological response at week 24 (i.e., HBV DNA > 300 copies/mL at week 24). Increasing from 37.1% to 48.6% (Table 1).

HBeAg seroconversion rates compared with other NAs, especially in suboptimal responder patients.31,34,36

From roadmap concept to roadmap model. The HBV DNA control during antiviral therapy will increase survival through prevention of disease progression and liver complications. Therefore, the goal of CHB treatment with NAs is to inhibit viral replication and to reduce HBV DNA to undetectable levels. In clinical practice, as drug resistance is associated with long-term NA use, optimizing the management of CHB has been shown to be crucial.41 As reported in the last decade, the roadmap concept based on early virological response at week 24 of therapy has been used as a strategy to predict better outcomes and reduce the risk of antiviral resistance (Fig. 1).32,43 The HBV DNA level at week 24 has been recently confirmed as a good marker for virological response.44

Using this well-established roadmap model, the telbivudine-based optimization strategy has shown benefits in patients with suboptimal early antiviral responses.20,21,45,46 In a multicenter, open-label, randomized, controlled study to assess the efficacy and safety of the telbivudine optimization strategy, the response rate (HBV DNA < 300 copies/mL (60 IU/mL)) was significantly higher for suboptimal responders in the telbivudine plus adefovir group compared with the telbivudine monotherapy group (71.7% vs 46.6%, respectively), after 2 years of treatment (Table 1).20 The rates of drug resistance were also significantly different between these two groups (0.5% vs 37.8%, respectively). In another study, after 2 years of telbivudine therapy, resistance rates were 25.8% and 10.8% in HBeAg-positive and HBeAg-negative patients, respectively, and lower rates (4.0% and 2.0%, respectively) were observed among patients who achieved undetectable serum HBV DNA levels at week 24 of therapy.41 Therefore, the roadmap model is considered a powerful tool to identify patients at risk of treatment failure and to reduce the risk of antiviral resistance (Fig. 1). These data support the use of telbivudine in combination with adefovir in suboptimal responders, to maximize response rates while minimizing the emergence of drug resistance. Moreover, as demonstrated by a cost-effectiveness analysis, both telbivudine and lamivudine roadmap models were cost-effective in HBeAg-positive patients at 2 years.47

were similar in both groups (85.3% vs 84.6%, P = 0.903, respectively), while genotypic resistance was significantly lower in patients receiving adefovir add-on therapy than in patients receiving telbivudine monotherapy (3.3% vs 42.5%, P < 0.001, respectively).38

Besides HBV DNA and ALT levels, quantitative hepatitis B core antibody (anti-HBc) has also been recently investigated as a potential predictor for treatment response in patients with CHB.40 In a retrospective study, patients treated with telbivudine who had a baseline anti-HBc ≥ 4.4 log10 IU/mL and baseline HBV DNA < 9 log10 copies/mL (2 × 108 IU/mL) achieved a higher rate of HBeAg seroconversion (37.1%) as compared with the unfavorable group (14.5%) at 2 years.39 The results were further improved when combining these baseline parameters with on-treatment response (HBV DNA level < 300 copies/mL (60 IU/mL) at week 24), increasing from 37.1% to 48.6% (Table 1).

Finally, even though telbivudine is not considered as a first-line drug for CHB, it has been associated with higher HBeAg seroconversion rates compared with other NAs, especially in suboptimal responder patients.31,34,36

ALT, alanine aminotransferase; CHB, chronic hepatitis B; DNA, deoxyribonucleic acid; HBc, hepatitis B core antibody; HBV, hepatitis B virus; PCR, polymerase chain reaction; ULN, upper limit of normal.
Safety profile of telbivudine

Overall safety profile. Telbivudine is generally well tolerated in patients with CHB.48 In the GLOBE study, the safety profile of telbivudine was shown to be comparable with that of lamivudine, with the exception of creatine kinase (CK) elevations, which were more frequent in telbivudine-treated patients.32 The observed CK elevations were mostly asymptomatic.32 In an open-label study including 655 patients, elevated serum CK occurred in 10.1% of patients, but most of these patients with asymptomatic CK elevations had spontaneous resolution without stopping telbivudine.37 In another study, telbivudine used as monotherapy or in combination with adefovir showed a satisfactory safety profile after 2 years of treatment.20

Although the mechanism remains elusive, telbivudine treatment has been associated with a significant improvement in renal function.49,50 This finding was further confirmed earlier this year by a systematic review showing that telbivudine (as monotherapy or combined with other NAs) can significantly improve renal function in patients with CHB, particularly those at high risk of renal impairment.51 Moreover, according to the latest update of the treatment algorithm for the management of CHB in the USA, a decline in renal function has been reported with the use of all approved NAs, with the exception of telbivudine.52

Safety profile in super-responders. When considering super-responder patients, telbivudine showed a good overall safety and tolerability profile (Table 2). In a real-world study, a small proportion of patients (7.8%) experienced adverse events and none was considered as severe.35 In another real-world study, there were no serious adverse events reported and telbivudine improved renal function after 1 year of treatment.34 In addition, the authors reported no significant difference in HCC development between telbivudine and entecavir.

Telbivudine use in pregnant women. Hepatitis B virus infection during pregnancy presents a risk for both the mother and the fetus. The treatment of HBV during pregnancy and prevention of mother-to-child transmission are considered to be the main challenges in this cohort.53 Vertical transmission of HBV accounts for most cases of CHB in endemic areas.54 The risk of developing CHB in infants is about 90%; mainly when the mother is positive for HBsAg and HBeAg.55 In addition, a maternal HBV DNA level > 200 000 IU/mL was identified as a risk factor for transmission.56

Although practice guidelines do not recommend the use of telbivudine as a first-line agent for the treatment of CHB, the European Association for the Study of the Liver and the Asian-Pacific Association for the Study of the Liver guidelines recommend telbivudine as one of the two preferred drugs to be used for the prevention of perinatal and intrauterine HBV transmission in the last trimester of pregnancy in HBsAg-positive women with high levels of viremia (serum HBV DNA > 10^6-7 IU/mL).22,33 Several studies showed that maternal treatment with telbivudine when compared with no treatment or placebo during the third trimester of pregnancy was effective in reducing vertical transmission of HBV infection.57-61 A meta-analysis of seven clinical trials involving 644 pregnant women demonstrated that telbivudine use during late pregnancy was effective in interrupting mother-to-child transmission in newborns.62 A recent
review including 1725 mothers treated with telbivudine during pregnancy showed that the rate of mother-to-child transmission was very low (0.7%). Also, these results showed a favorable safety profile of telbivudine and were consistent with other meta-analyses. As both telbivudine and tenofovir have been classified as Food and Drug Administration pregnancy risk category B drugs, they should be considered for the treatment of CHB during pregnancy. A recent meta-analysis including data on 3622 women showed that antiviral therapy during pregnancy reduced

### Table 2  Safety profile of telbivudine in super-responders

| References   | Study design/patients                                                                 | Safety results                                                                 |
|--------------|--------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Tsai et al.  | Retrospective study/CHB patients with virological resistance \( n = 230 \)           | No serious AEs were reported.                                                  |
| Wang et al.  | Prospective, open-label, multicenter study/CHB patients \( n = 116 \)                | Both creatinine and eGFR significantly improved in the telbivudine and entecavir groups after 1 year of treatment, but no significant difference was found at year 2. 9/116 (7.8%) patients experienced AEs. |
| Tsai et al.  | Prospective study/CHB patients \( n = 195 \)                                         | No severe AEs were reported.                                                    |
| Wang et al.  | Open-label extension study from GLOBE/015 studies/CHB patients \( n = 502 \)        | Telbivudine had an acceptable safety profile.                                  |
| Zeuzem et al.| Prospective, randomized, double-blind, phase 3 study/CHB patients \( n = 680 \)    | Most common drug-related AEs were increased serum creatine kinase (10.1%), headache (2.9%), nausea (2.0%), and fatigue (2.7%). Data on safety were not reported in this paper. |

AEs, adverse events; CHB, chronic hepatitis B; eGFR, estimated glomerular filtration rate.

### Table 3  Mother-to-child transmission and maternal outcomes at 6–12 months follow-up (adapted from Brown et al.67)

| References   | Telbivudine                                             | References   | Tenofovir                                             |
|--------------|---------------------------------------------------------|--------------|-------------------------------------------------------|
| **Mother-to-child transmission** | Reduction in infant HBsAg seropositivity versus control | Reduction in infant HBV DNA positivity versus control |                                                                 |
| 1 RCT and 3 case–control studies: | 15.8%                                                   | 3 Non-RCTs:  | 15.8%                                                 |
| Guo et al.68 |                                                          | Cen et al.69 |                                                        |
| Yao et al.70 |                                                          | Chen et al.71|                                                        |
| Zhang et al.60 |                                                        | Greenup et al.72|                                                      |
| Zhang73      |                                                        |                                                                 |
| **Maternal outcomes** | HBV DNA suppression versus control | ALT normalization versus control |                                                                 |
| 3 Non-RCTs:  | 35.4% versus 0%                                         | 2 Non-RCTs:  | 89.2% versus 1.25%                                    |
| Han et al.74 |                                                          | Cen et al.69 |                                                        |
| Han et al.61 |                                                          | Chen et al.71|                                                        |
| Pan et al.58 |                                                          |                                                                 |
| 2 Non-RCTs:  | 85.4% versus 58.3%                                      | 1 Non-RCT:   | 80.9% versus 62.5%                                    |
| Han et al.74 |                                                          | Cen et al.69 |                                                        |
| Pan et al.58 |                                                          |                                                                 |

ALT, alanine aminotransferase; HBsAg, hepatitis B surface antigen; RCT(s), randomized clinical trial(s).
mother-to-child transmission and improved HBV DNA suppression in patients with high viral loads. Infant HBsAg seropositivity and HBV DNA positivity were reduced by 15.8% and 16.2%, respectively, in the telbivudine group compared with the control group. Maternal HBV DNA suppression and ALT normalization were also improved (Table 3). Although there were insufficient controlled data, similar results were found for tenofovir compared with the control group (Table 3). Furthermore, a 2016 multicenter, open-label, randomized, parallel-group trial including 200 patients showed that the rate of mother-to-child transmission was lower with tenofovir therapy compared with usual care without antiviral therapy.

Conclusions and future perspective

The goal of CHB treatment with NAs is to control viral replication, leading to a reduction of HBV DNA to undetectable levels, reduction of serum ALT to normal levels, and loss of HBeAg in HBeAg-positive patients. Because of the various risks of drug resistance, several potential strategies for HBV suppression have been reported. HBV DNA undetectability by polymerase chain reaction at week 24 of therapy can predict virological responses in patients with CHB. This review describes the clinical benefits of the super-responders model; applying the model (higher baseline serum ALT, i.e. ALT levels ≥ 2×ULN, and lower baseline serum HBV DNA levels, i.e. HBV DNA levels <9 \(\log_{10}\) copies/mL (2 × 10^5 IU/mL) in HBeAg-positive patients, or HBV DNA <7 \(\log_{10}\) copies/mL (2 × 10^6 IU/mL) in HBeAg-negative patients) is associated with improved clinical outcomes with telbivudine. In addition, considering pre-treatment characteristics and on-treatment responses as an easy-to-use model for the clinician, telbivudine provides an option to effectively treat patients with CHB, especially those with or at risk of renal impairment, or women of childbearing age.

Nevertheless, management of patients with CHB remains unclear in specific conditions. Therefore, new randomized, clinical trials are warranted in patients with mild ALT and low HBV DNA levels (e.g. < 20000 IU/mL for HBeAg-positive and < 2000 IU/mL for HBeAg-negative patients) to determine the long-term benefit and safety profiles of anti-HBV therapies in the immune-tolerant phase. Novel agents targeting different steps of the HBV replication cycle should also be investigated in order to eradicate HBV infection.

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Telbivudine therapy for chronic hepatitis B

J-H Kao et al.

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