

Randomized Clinical Trial

Telbivudine vs tenofovir in hepatitis B e antigen-negative chronic hepatitis B patients: OPTIMA roadmap study

Zahari Krastev, Diana Petrova, Iskren Kotzev, Mustafa Kemal Celen, Meryl Mendelson, Richa Chandra, Priti Pandey, Kamal Hamed

Zahari Krastev, Clinic of Gastroenterology, St. Ivan Rilsky University Hospital, Medical University, Sofia 1606, Bulgaria

Diana Petrova, Department of Gastroenterology, University Hospital Alexandrovska, Sofia 1431, Bulgaria

Iskren Kotzev, Clinic of Hepatogastroenterology, University Hospital St Marina, Varna 9010, Bulgaria

Mustafa Kemal Celen, Infectious Disease Clinic, Dicle University, 21280 Diyarbakir, Turkey

Meryl Mendelson, Richa Chandra, Kamal Hamed, Novartis Pharmaceuticals Corporation, East Hanover, NJ 07936, United States

Priti Pandey, Novartis Healthcare Pvt. Ltd., Hyderabad 500081, India

Author contributions: All authors were involved in study conduct, data interpretation and defining the content for the manuscript; all authors had full access to data in the study, discussed the results, critically reviewed the draft manuscript and agreed on the final version.

Supported by Novartis Pharma AG.

Institutional review board statement: The study received approval from the Ethik-Kommission der Medizinischen Universität Wien und des Allgemeinen Krankenhauses der Stadt in Austria; Ethics Committee for Multicentre Trials in Bulgaria; RF MoHSD, Department of State Regulation of Circulation of Medicines, Ethics Council in Russia; National Ethics Committee for Clinical Trials in Greece; Comitato Etico Azienda Ospedaliera Universitaria Policlinico P. Giaccone in Italy; Institut Municipal D'Investigació mèdica in Spain; Ethik-Kommission der Albert-Ludwigs-Universität Freiburg in Germany; and Ege University Medical Faculty Clinical Research Ethics Committee in Turkey.

Informed consent statement: This study was conducted in accordance with the Declaration of Helsinki and good clinical practice guidelines. Written informed consent was obtained from

each patient before enrolment.

Conflict-of-interest statement: Krastev Z received fees for serving as a member of advisory board of Gilead, as well as research funding from Abbvie, Applied Clinical Pharmacology Services, Centocor, Comac Medical, Gilead, GSK, Idenix, Johnson and Johnson, Millennium Pharmaceuticals, MSD, Norgine, Novartis, Roche, Receptos and Schwabe; Petrova D received research funding from Aventis, Centocor, Gilead, GSK, Idenix, Johnson and Johnson, Norgine, Novartis and Roche; Kotzev I received lecture fees from Novartis; Celen MK has nothing to declare; Mendelson M, Chandra R and Hamed K are employees of Novartis Pharmaceuticals Corporation; Pandey P is an employee of Novartis Healthcare Pvt. Ltd.

Data sharing statement: No data were created, so no data are available.

Open-Access: This article is an open-access article, which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Unsolicited manuscript

Correspondence to: Kamal Hamed, MD, MPH, Sr Worldwide Medical Director, Novartis Pharmaceuticals Corporation, 1 Health Plaza, East Hanover, NJ 07936, United States. kamal.hamed@novartis.com
Telephone: +1-862-7781371
Fax: +1-973-7817153

Received: March 16, 2016
Peer-review started: March 18, 2016
First decision: April 19, 2016
Revised: May 6, 2016
Accepted: July 14, 2016
Article in press: July 18, 2016

Published online: November 18, 2016

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Abstract

AIM

To make efficacy and safety comparison of telbivudine-roadmap and tenofovir-roadmap in hepatitis B e antigen (HBeAg)-negative chronic hepatitis B (CHB) patients.

METHODS

This was the first prospective, randomised, two-arm, open-label, non-inferiority study in HBeAg-negative CHB patients that compared telbivudine and tenofovir administered as per roadmap concept. Patients were treated up to 24 wk and, depending on virologic response, continued the same therapy or received add-on therapy up to 104 wk. Eligible patients received an additional 52 wk of treatment in the extension period (*i.e.*, up to 156 wk). Patients who developed virologic breakthrough (VB) while on monotherapy also received add-on therapy. The primary efficacy endpoint was the rate of patients achieving hepatitis B virus (HBV) DNA < 300 copies/mL at week 52. Secondary efficacy endpoints included the rates of HBV DNA < 300 and < 169 copies/mL, HBV DNA change from baseline, alanine aminotransferase normalisation, hepatitis B surface antigen (HBsAg) loss, HBsAg seroconversion, VB, and emergence of resistance at various timepoints throughout the study. Safety and estimated glomerular filtration rate (eGFR) were also analysed.

RESULTS

A total of 241 patients were randomised. Non-inferiority of telbivudine arm to tenofovir arm was demonstrated at week 52 (± 7 d window), with over 91% of patients in each treatment arm achieving HBV DNA level < 300 copies/mL. Both arms were similar in terms of key secondary efficacy variables at weeks 104 and 156. The percentage of patients achieving HBV DNA < 300 copies/mL remained high and was similar in the telbivudine and tenofovir arms at both weeks 104 and 156. Over 82% of patients in both arms achieved alanine aminotransferase normalisation at week 52, and this percentage remained high at weeks 104 and 156. Telbivudine treatment progressively reduced serum HBsAg levels from baseline while no change was reported in quantitative HBsAg during therapy with tenofovir. Both treatments showed acceptable safety profiles. The telbivudine arm showed eGFR improvement unlike the tenofovir arm.

CONCLUSION

Efficacy was shown for both telbivudine-roadmap and tenofovir-roadmap regimens in HBeAg-negative CHB patients over 156 wk. Telbivudine arm was associated with renal improvement.

Key words: Chronic hepatitis B; Glomerular filtration rate; Telbivudine; Tenofovir; Roadmap concept

Core tip: This was the first prospective, randomised, non-inferiority study in hepatitis B e antigen-negative chronic hepatitis B patients that compared telbivudine and tenofovir administered as per roadmap concept. Both treatments based on the roadmap approach were effective over a 156 wk treatment period. Non-inferiority of telbivudine arm to tenofovir arm was demonstrated at week 52, with over 91% of patients in each treatment arm achieving hepatitis B virus DNA level < 300 copies/mL. Both treatments showed acceptable safety profiles. Moreover, telbivudine showed an improvement in estimated glomerular filtration rate from baseline.

Krastev Z, Petrova D, Kotzev I, Celen MK, Mendelson M, Chandra R, Pandey P, Hamed K. Telbivudine vs tenofovir in hepatitis B e antigen-negative chronic hepatitis B patients: OPTIMA roadmap study. *World J Hepatol* 2016; 8(32): 1402-1413 Available from: URL: <http://www.wjgnet.com/1948-5182/full/v8/i32/1402.htm> DOI: <http://dx.doi.org/10.4254/wjh.v8.i32.1402>

INTRODUCTION

Approximately 240-400 million people worldwide are chronically infected with hepatitis B virus (HBV), with a wide variation of prevalence among countries, and more than 780000 people die every year due to acute or chronic hepatitis B (CHB)^[1-3]. Although CHB may be treated with interferon or nucleos(t)ide analogue (NA) antivirals, emergence of resistance due to prolonged NA therapy or incomplete suppression of HBV still remains an important concern^[4]. Several studies have suggested that the use of response-guided add-on therapy is associated with a higher rate of virologic response and reduced antiviral resistance as compared to sequential monotherapy^[5,6].

Early virologic response has been used as a guide to predict better outcomes and to reduce the risk of antiviral resistance^[7,8]. As previously reported^[9,10], the roadmap concept uses early virologic response at week 24 to individualize ongoing management of CHB patients. Patients with a complete response at week 24 can remain on their initial therapy, whereas treatment modification that may include the addition of a second drug is done for those with an inadequate virologic response. This strategy is relevant mainly in patients receiving NA with a low genetic barrier to resistance (clevudine, emtricitabine, lamivudine, telbivudine)^[10]. In hepatitis B e antigen (HBeAg)-positive CHB patients treated with telbivudine, a response-guided treatment optimization strategy with telbivudine based on the roadmap concept has been demonstrated to improve the clinical outcomes of patients with a suboptimal antiviral response^[11,12].

The aim of this study, OPTIMA, was to assess the efficacy and safety of telbivudine and tenofovir regimens,

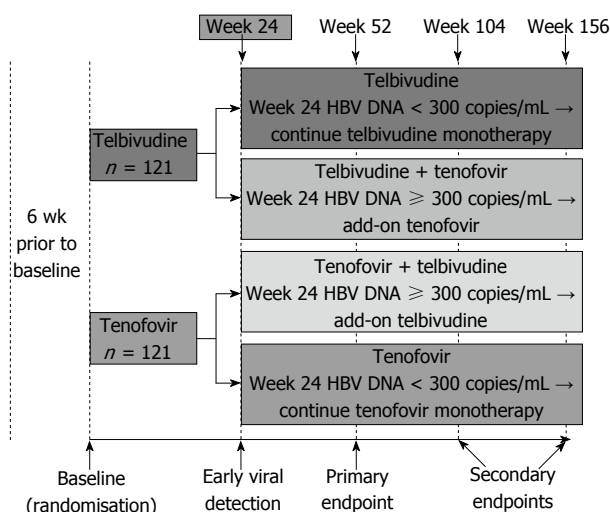


Figure 1 Study design. HBV: Hepatitis B virus.

when administered using the roadmap concept, in HBeAg-negative patients with CHB. This was the first study that compared efficacy of the 2 regimens in a prospective manner. The safety of the combination of telbivudine and tenofovir, for which limited data are currently available, was also evaluated.

MATERIALS AND METHODS

Study design and conduct

OPTIMA was a prospective, randomised, 2-arm, open-label study (ClinicalTrials.gov ID: NCT01379508) that enrolled patients between February 2011 and October 2012 in 8 countries (Austria, Bulgaria, Germany, Greece, Italy, Russia, Spain and Turkey). This study was approved by the Institutional Review Board at each participating centre, and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Written informed consent was obtained from each patient before enrolment.

Eligible patients were randomised *via* an interactive voice response system in a 1:1 ratio to either telbivudine arm (600 mg/d) or tenofovir arm (300 mg/d) (Figure 1). Randomisation was stratified by the screening HBV DNA level ($< 7 \log_{10}$ copies/mL or $\geq 7 \log_{10}$ copies/mL) and alanine aminotransferase (ALT) level [$< 3 \times$ upper limit of normal (ULN) or $\geq 3 \times$ ULN].

This study used the response-guided add-on strategy (roadmap concept). For patients with HBV DNA ≥ 300 copies/mL (≥ 51 IU/mL) at week 24, tenofovir was added to telbivudine by week 26 in the telbivudine arm, and telbivudine was added to tenofovir by week 26 in the tenofovir arm. For patients with HBV DNA < 300 copies/mL at week 24, telbivudine and tenofovir monotherapies in the respective arms were continued. Patients who developed virologic breakthrough (VB) while on monotherapy received add-on therapy. However, patients who developed VB after week 24 while on combination therapy were discontinued from the study.

Patients

Eligible patients were male or female ≥ 18 years of age, with detectable hepatitis B surface antigen (HBsAg) for ≥ 6 mo, HBeAg-negative with positive hepatitis B e antibody, available liver histology report within 12 mo before screening compatible with CHB (patients without evaluable liver histology were eligible if they had clinical evidence of compensated liver cirrhosis or non-invasive methods that support the diagnosis of moderate to severe liver inflammation and/or fibrosis), serum HBV DNA > 2000 IU/mL, and serum ALT level $> 1 \times$ ULN and $< 10 \times$ ULN at the screening visit. Patients with ALT $\leq 1 \times$ ULN at screening were eligible if they had at least moderate liver inflammation or fibrosis, clinical evidence of compensated cirrhosis, or ALT level $> 1 \times$ ULN within the last 6 mo.

Main exclusion criteria included co-infection with hepatitis C virus, hepatitis D virus or human immunodeficiency virus; hepatic decompensation; liver disease other than CHB; any nucleos(t)ide or interferon/immunomodulator treatment in the previous 6 mo; chronic renal insufficiency or serum creatinine clearance < 50 mL/min; history of myopathy, myositis, or persistent muscle weakness; pregnant or nursing (lactating) women; or history of malignancy of any organ system (other than localized basal cell carcinoma of the skin).

Patients were allowed to receive an additional 52 wk of treatment in the extension period (*i.e.*, up to 156 wk) if they had HBV DNA < 300 copies/mL at both weeks 92 and 104, and serum creatinine clearance ≥ 50 mL/min at two consecutive visits including week 104.

Efficacy and safety analyses

The primary efficacy endpoint was the rate of patients achieving HBV DNA < 300 copies/mL (51 IU/mL) at week 52. Secondary efficacy endpoints included the rates of patients with HBV DNA < 300 copies/mL at weeks 104 and 156, and HBV DNA < 169 copies/mL (29 IU/mL) (lower limit of detection) at weeks 24, 52, 104 and 156; change from baseline in HBV DNA; ALT normalisation at weeks 52, 104 and 156; HBsAg loss and HBsAg seroconversion; VB; and emergence of resistance. In addition, subgroup analyses were performed for secondary efficacy endpoints by baseline HBV DNA (*i.e.*, $< 7 \log_{10}$ copies/mL or $\geq 7 \log_{10}$ copies/mL).

VB was defined as an increase of HBV DNA by at least $1 \log_{10}$ copies/mL (or $1 \log_{10}$ IU/mL) above nadir on 2 consecutive visits, or at the last on-treatment visit in patients who did not have a primary non-response. Emergence of resistance was assessed as the rate of confirmed treatment-emergent genotypic resistance and was assessed at the time of confirmed VB and at week 24 in patients with viral load ≥ 300 copies/mL, it was calculated cumulatively at weeks 52, 104 and 156.

HBV DNA detection and quantification were performed at a central laboratory using the COBAS TaqMan real-time polymerase chain reaction assay (Roche Molecular Systems, Branchburg, NJ, United States).

Safety assessments included monitoring of adverse events (AEs), vital signs, and graded laboratory abnormalities. Estimated glomerular filtration rate (eGFR), calculated by the modification of diet in renal disease formula was recorded. AEs of special interest (muscle and renal function related events) were also reported.

Statistical analysis

For the primary efficacy analysis, study treatments were compared for non-inferiority.

Based on the assumptions of 96% and 97% HBV DNA < 300 copies/mL at week 52 in the telbivudine arm and the tenofovir arm, respectively, and an approximately 10% dropout rate, it was estimated that 120 randomised patients per arm would provide 87% power for the non-inferiority testing on the primary analysis. Non-inferiority in efficacy of telbivudine arm to tenofovir arm was to be claimed if the lower limit of the 2-sided confidence interval (CI) for the difference was above the pre-determined non-inferiority margin (-10%).

A weighted Cochran-Mantel-Haenszel method, adjusting for randomisation strata [HBV DNA (< or $\geq 7 \log_{10}$ copies/mL) and ALT (< or $\geq 3 \times$ ULN) levels], was used to assess comparative therapeutic response rates.

For continuous variables, summary statistics of absolute value and of change from baseline, including mean, standard deviation (SD), median, minimum, and maximum were used. For dichotomous endpoints, statistical summaries included count and percentage of patients with a positive response (response rate) and also 95%CI for the response rate.

The intent-to-treat (ITT) population consisted of all patients who received at least one dose of study drug and had at least one post-baseline assessment of serum HBV DNA. The roadmap ITT (rITT) population consisted of all patients who did not discontinue before week 24 and did not deviate from the protocol defined rules of receiving add-on at week 24 (*i.e.*, patients who received the add-on therapy at week 24 if they had HBV DNA ≥ 300 copies/mL, or did not receive the add-on at week 24 if they had HBV DNA < 300 copies/mL). The modified ITT (mITT) population consisted of all patients in the ITT population who were eligible and enrolled in the extension period beyond week 104. The per-protocol population consisted of all patients in the ITT population who had no major protocol deviations.

All efficacy observations on or after censoring date were treated as missing. A patient's censoring date was the date of the first occurrence of: One day after the last dose of the study drug, the start of first prohibited CHB-related medication, pregnancy, or a specific major protocol deviation. To assess the robustness of the results due to missing data, the analysis of primary and all secondary efficacy endpoints were performed based on the rITT and ITT analysis populations. The mITT population was used only for the week 156 analysis.

The primary efficacy endpoint (week 52) analysis was performed on the rITT population. The analyses presented include: (1) assessments within the ± 7 d protocol-pre-

specified visit window around the scheduled week 52 date; (2) missing data at week 52 treated as failure; (3) missing data imputed using the earliest available assessment within the 28 d window starting from the scheduled week 52 date; and (4) missing data imputed using the last observation carried forward (LOCF).

Secondary efficacy parameters including HBV DNA, ALT normalisation, HBsAg loss, and HBsAg seroconversion were analysed using two imputation methods for missing data: (1) missing data treated as failure; and (2) missing data imputed using the earliest available assessment within the 28 d window starting from the scheduled visit for weeks 52 (except HBV DNA < 300 copies/mL), 104 and 156. VB and eGFR were analysed using the LOCF imputation method for missing data. Treatment-emergent genotypic resistance was analysed using cumulative imputation method for missing data. Missing eGFR assessments were imputed using the LOCF method.

Analyses of endpoints using LOCF imputation at weeks 104 and 156 are presented for the rITT and mITT populations, respectively.

RESULTS

Study patients

A total of 241 patients (121 in the telbivudine arm and 120 in the tenofovir arm) were randomised in this study. A total of 22 (18.2%) patients in the telbivudine arm and 13 (10.8%) patients in the tenofovir arm discontinued prematurely from the study. The most common reasons for discontinuation in the telbivudine arm were consent withdrawal ($n = 7$), lost to follow-up ($n = 5$), and administrative reasons ($n = 4$). In the tenofovir arm, the most common reasons for discontinuation were AEs ($n = 5$), consent withdrawal ($n = 4$), and lost to follow-up ($n = 3$).

Major protocol deviations were reported in 11 (9.1%) patients in the telbivudine arm and 8 (6.7%) patients in the tenofovir arm. The most commonly reported major deviations were patients on monotherapy with confirmed VB not starting add-on therapy within 2 wk of laboratory confirmation of VB ($n = 9$), patients with a positive HBeAg result ($n = 6$), and patients not completing 3 wk of treatment before the third visit ($n = 4$).

The safety population comprised 120 patients in each of the 2 treatment arms. One patient in the telbivudine arm was excluded from the safety population as this patient did not receive any study treatment. Of the 241 randomized patients, 235 patients were included in the ITT population, with 117 (96.7%) in the telbivudine arm and 118 (98.3%) in the tenofovir arm. Six patients were excluded from the ITT population (4 patients in the telbivudine arm due to no post-baseline HBV DNA assessments, non-compliance with the study conduct, or no study treatment received; and 2 patients in the tenofovir arm because of no post-baseline HBV DNA assessments and viral resistance at baseline). A total of 113 (93.4%) patients in the telbivudine arm and 117 (97.5%) patients in the tenofovir arm comprised the

Table 1 Demographic and baseline characteristics, randomised population

Patients characteristics	Telbivudine (<i>n</i> = 121)	Tenofovir (<i>n</i> = 120)
Age, mean (SD), yr	42.1 (11.5)	43.3 (12.6)
Median (min-max)	42.0 (19-70)	44.0 (18-73)
Male gender, <i>n</i> (%)	86 (71.1)	82 (68.3)
Race, Caucasian, <i>n</i> (%)	117 (96.7)	118 (98.3)
Body mass index, mean (SD), kg/m ²	25.8 (4.1)	25.7 (4.0)
Median (min-max)	25.6 (16.5-40.4)	25.2 (18.4-39.8)
Genotype, <i>n</i> (%)		
A	6 (5.0)	2 (1.7)
B	1 (0.8)	0 (0.0)
C	0 (0.0)	1 (0.8)
D	104 (86.0)	110 (91.7)
G	1 (0.8)	0 (0.0)
Other	1 (0.8)	0 (0.0)
Unknown	8 (6.6)	7 (5.8)
HBV DNA, mean (SD), log ₁₀ copies/mL	6.2 (1.5)	6.0 (1.4)
Median (min-max)	6.1 (3.2-9.5)	5.9 (2.5-9.9)
< 7 log ₁₀ , <i>n</i> (%)	85 (70.2)	86 (71.7)
≥ 7 log ₁₀ , <i>n</i> (%)	36 (29.8)	34 (28.3)
Serum alanine aminotransferase, mean (SD), IU/L	79.8 (84.1)	78.2 (86.1)
Median (min-max)	53.0 (13-494)	49.0 (5-568)
Serum aspartate aminotransferase, mean (SD), IU/L	54.0 (52.8)	52.5 (47.1)
Median (min-max)	35.0 (13-347)	35.0 (13-322)
Creatine phosphokinase, mean (SD), IU/L	118.6 (64.4)	160.1 (299.3)
Median (min-max)	104.0 (35-430)	111.0 (36-2976)
eGFR ¹ , mean (SD), (mL/min per 1.73 m ²)	97.4 (17.9)	95.8 (16.4)
Median (min-max)	96.6 (60.9-147.1)	94.2 (60.5-138.4)

¹eGFR: Estimated glomerular filtration rate (modification of diet in renal disease formula). HBV: Hepatitis B virus; SD: Standard deviation.

rITT population. Five patients (4 in the telbivudine arm and 1 in the tenofovir arm) that were included in the ITT population were excluded from the rITT population because they discontinued before week 24 and were not eligible for or enrolled into the roadmap concept period (weeks 24 to 104).

The per-protocol population consisted of 107 (88.4%) patients in the telbivudine arm and 111 (92.5%) patients in the tenofovir arm. A total of 17 patients (10 in the telbivudine arm and 7 in the tenofovir arm) were included in the ITT and rITT populations but were excluded from the per-protocol population because of major protocol deviations. The mITT population consisted of 79 (65.3%) patients in the telbivudine arm and 89 (74.2%) patients in the tenofovir arm.

Treatment arms were balanced with respect to demographics and baseline characteristics, with no clinically meaningful differences between the telbivudine and tenofovir arms (Table 1). Most (86.0% telbivudine, 91.7% tenofovir) patients were infected with HBV genotype D, and the mean HBV DNA at baseline was 6.2 log₁₀ copies/mL in the telbivudine arm and 6.0 log₁₀ copies/mL in the tenofovir arm, with 70.2% and 71.7% of patients, respectively, having a baseline HBV DNA < 7 log₁₀ copies/mL.

Primary efficacy endpoint

Virologic response (HBV DNA < 300 copies/mL) at week 52 was achieved in more than 91% of patients in each treatment arm (Figure 2A). The primary endpoint

analysis showed that the antiviral efficacy of telbivudine-roadmap was non-inferior to that of tenofovir-roadmap application at week 52 in the rITT population; the lower bound of the 95%CI for the difference between the 2 treatment arms was above the non-inferiority margin of -10%: -9.4% (utilizing assessments within the ±7 d protocol-prespecified visit window); -8.3% for the 28 d window imputation; and -7.9% for the LOCF imputation. Using missing data as treatment failure, non-inferiority was not demonstrated (lower bound of the 95%CI: -10.5%, just below the protocol defined non-inferiority margin) (Table 2). In this analysis, HBV DNA samples from 6 patients (4 in the telbivudine arm and 2 in the tenofovir arm), although resulted in < 300 copies/mL, were considered as missing because they were not obtained at the week 52 visit date itself (*i.e.*, patients were counted as treatment failures).

The primary endpoint analysis at week 52 in the per-protocol population supported the non-inferiority of the telbivudine arm to the tenofovir arm (98.0% in the telbivudine arm and 99.0% in the tenofovir arm, lower bound of the 95%CI: -4.3%).

Secondary efficacy endpoints

Virologic responses: Percentage of patients achieving HBV DNA < 300 copies/mL (51 IU/mL) at weeks 24 and 104, and by baseline viral load at weeks 24, 52 and 104 in the rITT population: The percentage of patients achieving HBV DNA < 300 copies/mL in the telbivudine and tenofovir arms at week 24 was 80.5% and 89.7%,

Table 2 Virologic response, roadmap intent-to-treat population

Parameters	Telbivudine (<i>n</i> = 113)	Tenofovir (<i>n</i> = 117)	Difference between arms and 95%CI
Patients achieving HBV DNA < 300 copies/mL (51 IU/mL) at week 52, <i>n</i> (%)			
± 7 d protocol-prespecified visit window	104 (91.9)	111 (95.0)	-3.1% (-9.4%, 3.1%) ¹
Treating missing as failure	103 (91.0)	111 (95.0)	-4.0% (-10.5%, 2.5%) ¹
28 d imputation	105 (92.7)	111 (95.0)	-2.3% (-8.3%, 3.8%) ¹
Last observation carried forward	108 (95.4)	116 (99.2)	-3.8% (-7.9%, 0.4%) ¹
Change from baseline in HBV DNA levels (log ₁₀ copies/mL) by visit, mean (SD)			<i>P</i> -value
Week 24	-4.001 (1.256)	-4.122 (1.165)	<i>P</i> < 0.0001 ²
Week 52	-4.356 (1.473)	-4.305 (1.343)	<i>P</i> < 0.0001 ²
Week 104	-4.281 (1.753)	-4.349 (1.382)	<i>P</i> < 0.0001 ²

¹Percentages and 95%CI were calculated using Mantel-Haenszel weighted estimates stratified by baseline HBV DNA and alanine aminotransferase levels;

²*P*-values were calculated using paired *t*-test comparing post-baseline timepoints to baseline timepoints. CI: Confidence interval; HBV: Hepatitis B virus; SD: Standard deviation.

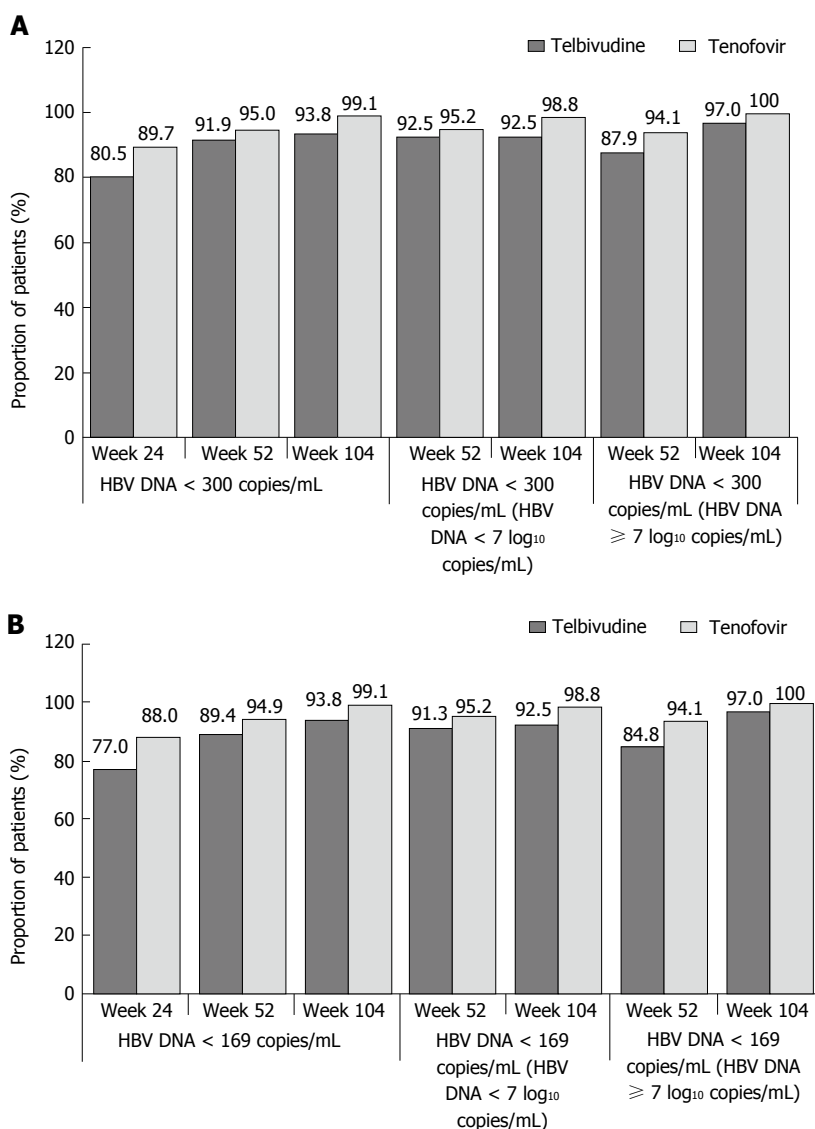


Figure 2 Proportions of patients achieving hepatitis B virus DNA < 300 (A) or < 169 copies/mL (B), by visit and by baseline hepatitis B virus DNA levels (< 7 or ≥ 7 log₁₀ copies/mL), roadmap intent-to-treat population. HBV: Hepatitis B virus.

and at week 104, 93.8% and 99.1%, respectively (Figure 2A).

In patients with lower baseline viral load (HBV DNA level < 7 log₁₀ copies/mL) at week 24, telbivudine and

tenofovir regimens were similar in terms of viral load reduction with 93.8% and 95.2% of patients achieving HBV DNA levels < 300 copies/mL in the telbivudine and tenofovir arms, respectively. At weeks 52 and

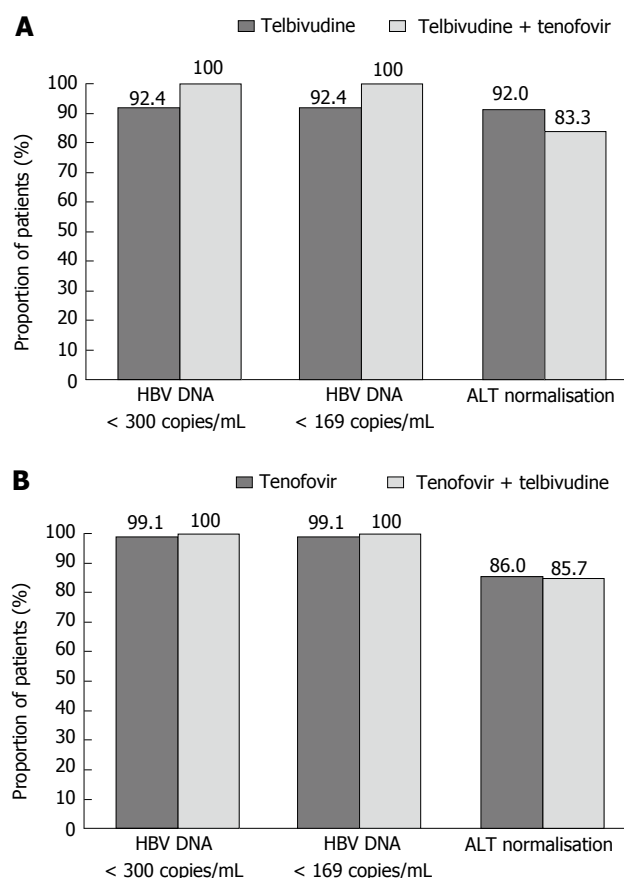


Figure 3 Intensification with tenofovir (A) or telbivudine (B), virologic response and aminotransferase normalisation at week 104, roadmap intent-to-treat population. ALT: Alanine aminotransferase; HBV: Hepatitis B virus.

104, telbivudine and tenofovir regimens seemed to be similar in terms of viral load reduction, with over 92% of patients achieving HBV DNA levels < 300 copies/mL at weeks 52 and 104 (Figure 2A). The proportion of patients in each arm with higher baseline viral load ($\geq 7 \log_{10}$ copies/mL) was relatively small to make any meaningful interpretation.

Change from baseline in HBV DNA levels from week 24 to week 104 in the rITT population: A statistically significant ($P < 0.0001$) reduction in HBV DNA levels vs baseline was achieved in both treatment arms at week 24 and was sustained through week 104 (Table 2).

Intensification with tenofovir or telbivudine for HBV DNA ≥ 300 copies/mL at week 24 or for VB post week 24 through week 104 in the rITT population; response at week 104 (HBV DNA < 300 copies/mL) according to the requirement for add-on therapy at week 24: A greater number of patients in the telbivudine arm required add-on therapy compared with the tenofovir arm (35 patients in the telbivudine arm including 22 patients requiring add-on therapy at week 24 and 13 requiring add-on therapy post week 24 vs 11 patients in the tenofovir arm, all requiring add-on therapy at week 24).

The proportion of patients in the telbivudine arm achieving HBV DNA < 300 copies/mL at week 104 was greater in those who required tenofovir add-on therapy at week 24 (100%, 21/21 patients) than patients who

were in the telbivudine monotherapy group following the week 24 visit (92.4%, 85/92 patients) (Figure 3A).

The proportion of patients in the tenofovir arm achieving HBV DNA < 300 copies/mL at week 104 was similar in those who required telbivudine add-on therapy at week 24 (100%, 11/11 patients) to those who were in the tenofovir monotherapy group following the week 24 visit (99.1%, 105/106 patients) (Figure 3B).

Percentage of patients achieving HBV DNA < 169 copies/mL (29 IU/mL) at weeks 24, 52 and 104 in the rITT population: The rate of patients achieving HBV DNA < 169 copies/mL at weeks 24, 52 and 104 was consistent with that observed for the endpoint of HBV DNA < 300 copies/mL (Figure 2B).

Percentage of patients achieving HBV DNA < 169 copies/mL at week 104 in the rITT population according to the requirement for add-on therapy at week 24: The proportion of patients in the telbivudine and tenofovir arms achieving HBV DNA < 169 copies/mL at week 104 and receiving add-on therapy were 7.6 and 0.9 percentage points greater, respectively, than patients who received monotherapy (Figure 3).

Maintained virologic responses at week 156 in the mITT population: The percentage of patients who maintained HBV DNA < 300 copies/mL at week 156 was similar in the telbivudine and tenofovir arms: 91.1% (72/79 patients) and 100% (89/89 patients), respectively, using LOCF imputation. Similar results were found in patients maintaining HBV DNA < 169 copies/mL [91.1% (72/79 patients) and 96.6% (86/89 patients), respectively].

HBsAg loss and HBsAg seroconversion: HBsAg loss and HBsAg seroconversion were not observed in any patient from either treatment arm at weeks 52, 104 or 156. Telbivudine treatment progressively reduced serum HBsAg levels (mean \pm SD) from baseline in the rITT population [$-0.116 \pm 0.581 \log_{10}$ IU/mL at week 52 ($P = 0.0368$) and $-0.179 \pm 0.633 \log_{10}$ IU/mL at week 104 ($P = 0.0032$)]. In contrast, no change was reported in quantitative HBsAg during therapy with tenofovir [$-0.038 \pm 0.349 \log_{10}$ IU/mL at week 52 ($P = 0.2399$) and $-0.030 \pm 0.385 \log_{10}$ IU/mL at week 104 ($P = 0.4063$)]. At week 156, change from baseline in HBsAg levels in the mITT population was $-0.204 \pm 0.759 \log_{10}$ IU/mL ($P = 0.0193$) in the telbivudine arm and $-0.031 \pm 0.412 \log_{10}$ IU/mL ($P = 0.4760$) in the tenofovir arm.

Biochemical response: ALT normalisation at weeks 52 and 104 in the rITT population: ALT levels significantly improved vs baseline in both treatment arms, with over 82% of patients in both arms achieving ALT normalisation at week 52 that was sustained up until week 104 (89.7% and 85.9% in the telbivudine and tenofovir arms, respectively) (Figure 4).

The results at week 104 by baseline viral load are presented in Figure 4.

ALT normalisation at week 104 in the rITT population according to the requirement for add-on therapy at week 24: The proportion of patients who achieved ALT

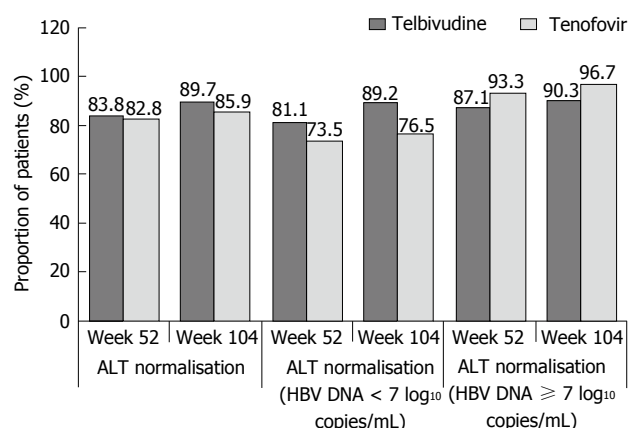


Figure 4 Proportions of patients achieving aminotransferase normalisation, by visit and by baseline hepatitis B virus DNA levels (< 7 or ≥ 7 log₁₀ copies/mL), roadmap intent-to-treat population. ALT: Alanine aminotransferase; HBV: Hepatitis B virus.

normalization at week 24 was higher (telbivudine arm) or similar (tenofovir arm) in patients who received add-on therapy (Figure 3).

Maintained biochemical response at week 156 in the mITT population: ALT normalisation was maintained in 92.0% of patients in the telbivudine arm and 91.1% of patients in the tenofovir arm.

Patients experiencing VB and emergence of resistance in the rITT and mITT populations:

At weeks 52 and 104, respectively, in the rITT population, cumulative rates of VB were reported in 2.7% (3/113) and 9.7% (11/113) of patients in the telbivudine arm (3.3% and 12.4% in the monotherapy group, none in the add-on treatment group). In the tenofovir arm, no patients developed VB cumulatively at week 52 and 1.7% (2/117) of patients developed VB cumulatively at week 104.

At week 52, cumulative emergence of resistance was reported in 2.7% (3/113) of patients in the telbivudine arm (3.3% in the monotherapy group, none in the add-on treatment group) and no treatment-emergent resistance was observed in the tenofovir arm. At week 104, cumulative emergence of resistance was reported in 7.4% (8/108) of patients in the telbivudine arm (9.2% in the monotherapy group, none in the add-on treatment group) and none in the tenofovir arm.

In the telbivudine arm, 10 patients experienced VB and 5 had emergence of resistance between weeks 104 and 156 in the mITT population. In the tenofovir arm, only 1 patient had VB and none developed viral resistance. The cumulative rate of VB at week 156 was 16.5% (13/79) in the telbivudine arm, and 1.1% (1/89) in the tenofovir arm. Cumulative rates of resistance were 10.8% (8/74) in the telbivudine arm (14.0% in the monotherapy group, none in the add-on treatment group) and none in the tenofovir arm.

Safety

No patients died or experienced ALT flare during the

study. The overall incidence of serious AEs (SAEs) was similar in the telbivudine arm and in the tenofovir arm [11 (9.2%) patients and 13 (10.8%) patients, respectively]. One patient in the tenofovir arm reported drug-related SAEs [moderately increased blood creatine phosphokinase (CPK), mild arthralgia, and moderate fatigue], which led to temporary interruption of the study drug (Table 3). There were no cases of myositis or myopathy.

Two patients in the telbivudine arm and 5 patients in the tenofovir arm discontinued due to AEs [myalgia and hepatocellular carcinoma (HCC) for telbivudine; headache, HCC, hepatic cirrhosis, cholestatic jaundice, and breast cancer for tenofovir], which were assessed by the investigator as unrelated to the study drugs. Most AEs were mild to moderate in severity. The proportion of patients reporting at least 1 AE, regardless of study drug relationship, was similar for telbivudine and tenofovir arms. The overall incidence of AEs suspected to be related to study drug was somewhat higher in the telbivudine arm compared with the tenofovir arm. The most frequent (≥ 2%) drug-related AEs reported in both arms are described in Table 3. Increased blood CPK levels [31 (25.8%) patients], myalgia [8 (6.7%) patients, and nausea 8 (6.7%) patients] were the drug-related AEs that were observed more frequently in the telbivudine arm compared with the tenofovir arm [16 (13.3%), 0, and 2 (1.7%) patients, respectively]. AEs of special interest were observed in 46 (38.3%) patients in the telbivudine arm and 27 (22.5%) patients in the tenofovir arm. These included elevated blood CPK and myalgia as the most commonly reported AEs in the telbivudine arm, and elevated blood CPK and ALT as the most commonly reported AEs in the tenofovir arm. Myalgia suspected to be drug related was reported in the telbivudine arm. The number of patients experiencing at least 1 muscle event along with 1 new-onset abnormal CPK episode during the study was greater in the telbivudine arm (Table 3).

The telbivudine arm showed a higher incidence of Grade 3/4 CPK elevations during the study than the tenofovir arm [19 (15.8%) patients vs 5 (4.2%) patients, respectively]. All Grade 3/4 CPK elevations were resolved (Table 3).

Telbivudine monotherapy (as of week 24) was associated with a significant improvement in eGFR as compared with tenofovir monotherapy (as of week 24). At week 24, the telbivudine monotherapy showed a statistically significant ($P = 0.0798$) improvement from baseline in eGFR compared to worsening with tenofovir monotherapy, with least squares mean percentage changes from baseline of 2.46% vs -1.17%, respectively. Further improvement in eGFR in the telbivudine monotherapy group (as of week 24) was observed at weeks 52 (4.90% vs -2.68% with tenofovir, $P = 0.0098$), 104 (5.54% vs -5.36%, $P < 0.0001$, respectively), and 156 (9.55% vs -6.23%, $P < 0.0001$, respectively) (Figure 5).

There was no significant change in vital signs from baseline for either treatment arm.

Table 3 Summary of safety results, safety population *n* (%)

Safety parameters	Telbivudine			Tenofovir		
	Monotherapy (<i>n</i> = 98)	Intensification with tenofovir (<i>n</i> = 22)	Overall (<i>n</i> = 120)	Monotherapy (<i>n</i> = 109)	Intensification with telbivudine (<i>n</i> = 11)	Overall (<i>n</i> = 120)
Any AE	69 (70.4)	17 (77.3)	86 (71.7)	75 (68.8)	8 (72.7)	83 (69.2)
AE related to drug	36 (36.7)	11 (50.0)	47 (39.2)	21 (19.3)	6 (54.5)	27 (22.5)
AE leading to drug discontinuation	2 (2.0)	0 (0.0)	2 (1.7)	5 (4.6)	0 (0.0)	5 (4.2)
Any SAE	6 (6.1)	5 (22.7)	11 (9.2)	11 (10.1)	2 (18.2)	13 (10.8)
SAE related to drug	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)	1 (0.8)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AEs related to drug occurring in $\geq 2\%$ of patients in any treatment arm						
Blood CPK increased	23 (23.5)	8 (36.4)	31 (25.8)	13 (11.9)	3 (27.3)	16 (13.3)
Nausea	6 (6.1)	2 (9.1)	8 (6.7)	0 (0.0)	2 (18.2)	2 (1.7)
Myalgia	7 (7.1)	1 (4.5)	8 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)
Alanine aminotransferase increased	2 (2.0)	0 (0.0)	2 (1.7)	3 (2.8)	1 (9.1)	4 (3.3)
Proteinuria	2 (2.0)	0 (0.0)	2 (1.7)	4 (3.7)	0 (0.0)	4 (3.3)
Aspartate aminotransferase increased	3 (3.1)	0 (0.0)	3 (2.5)	2 (1.8)	0 (0.0)	2 (1.7)
Any AE of special interest	35 (35.7)	11 (50.0)	46 (38.3)	23 (21.1)	4 (36.4)	27 (22.5)
AEs of special interest occurring in $\geq 2\%$ of patients in any treatment arm						
Blood CPK increased	24 (24.5)	10 (45.5)	34 (28.3)	17 (15.6)	3 (27.3)	20 (16.7)
Myalgia	10 (10.2)	2 (9.1)	12 (10.0)	2 (1.8)	1 (9.1)	3 (2.5)
Alanine aminotransferase increased	5 (5.1)	0 (0.0)	5 (4.2)	5 (4.6)	1 (9.1)	6 (5.0)
Proteinuria	3 (3.1)	0 (0.0)	3 (2.5)	4 (3.7)	0 (0.0)	4 (3.3)
Any patient with muscle event	12 (12.2)	2 (9.1)	14 (11.7)	2 (1.8)	1 (9.1)	3 (2.5)
Experiencing new-onset Grade 3/4 abnormal CPK within the study	4 (4.1)	1 (4.5)	5 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)
Experiencing new-onset Grade 1/2 abnormal CPK within the study	6 (6.1)	1 (4.5)	7 (5.8)	1 (0.9)	1 (9.1)	2 (1.7)
Any patient with new-onset Grade 3/4 CPK episode within the study	17 (17.3)	2 (9.1)	19 (15.8)	3 (2.8)	2 (18.2)	5 (4.2)
Episode not resolved	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

AE: Adverse event; CPK: Creatine phosphokinase; SAE: Serious adverse event.

DISCUSSION

NAs given as a single daily oral dose are considered the mainstay of CHB treatment^[13]. In clinical practice, attaining optimal efficacy with a low emergence of drug resistance remains an important goal^[14]. The roadmap concept utilizing add-on therapy for patients who do not achieve HBV DNA < 300 copies/mL at week 24 (in particular for agents with lower barriers to resistance) has been identified as a strategy to achieve this goal. This study was the first prospective, randomised clinical trial using the roadmap concept in HBeAg-negative CHB patients comparing efficacy and safety of telbivudine with tenofovir. As previously reported^[15], early detection of virologic response may be a useful guide to individualize CHB treatment. This study confirmed that monitoring virologic response at week 24 is a strong predictor of the treatment response by week 104^[16]. These data were consistent with an earlier study comparing telbivudine with lamivudine^[15].

In the real-world setting, use of the roadmap concept may offer several advantages such as early identification of patients with suboptimal responses to initiate an appropriate change in therapy^[10,11], and to provide clinicians with options for individualized treatment decisions^[5]. Although emergence of resistance had been identified as

an issue for HBeAg-negative CHB patients treated with telbivudine monotherapy^[15,17], the data from our study suggest that the risk for resistance is lower if telbivudine is administered using the roadmap concept, as compared to the GLOBE trial showing higher rates of resistance^[15]. Moreover, despite a somewhat higher percentage of patients requiring add-on therapy in the telbivudine arm, the overall efficacy profile of the 2 roadmap approach arms was comparable, as assessed by the percentages of patients achieving HBV DNA levels < 300 or < 169 copies/mL, and ALT normalisation at weeks 52, 104 and 156. Moreover, telbivudine treatment resulted in a statistically significant reduction in serum HBsAg levels from baseline while no change was reported in quantitative HBsAg during therapy with tenofovir.

Overall, both treatments based on the roadmap concept were well tolerated over the 156 wk treatment period in HBeAg-negative patients. Although myalgia and elevated blood CPK levels were reported in a higher number of patients in the telbivudine arm, the rates were consistent with the findings reported earlier in the literature^[12,15,18,19]. It is recommended that serum CPK levels should be monitored closely during treatment with telbivudine^[20].

Renal safety issues with oral NAs have been well-documented^[21-23]. Particularly, adefovir is considered to

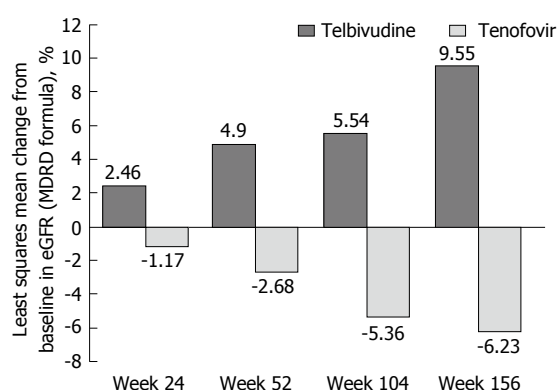


Figure 5 Changes in estimated glomerular filtration rate over time with telbivudine and tenofovir, safety population. eGFR: Estimated glomerular filtration rate; MDRD: Modification of diet in renal disease.

have high potential for nephrotoxicity and tenofovir has been associated with this risk^[24]. In our study, telbivudine was associated with improvement in eGFR from baseline to week 156 compared to the increasing deterioration over time with tenofovir. The finding of improvement in eGFR with telbivudine treatment was consistent with that reported in previous studies where telbivudine significantly improved while adefovir and lamivudine worsened renal function^[25,26]. CHB patients with impaired renal function at baseline have also shown an eGFR improvement after 1 year^[27] and 2 years of treatment with telbivudine^[11,28]. Similar results for telbivudine have also been reported in patients with cirrhosis, patients with compensated cirrhosis, or patients with no cirrhosis^[29,30]. These findings imply that telbivudine may offer benefit in patients with known or at risk of renal impairment. Although telbivudine improves renal function, the mechanism of this renal protective effect remains to be determined^[31].

The main limitations of the study are related to its design (open-label) and the relatively small sample size.

In conclusion, this study was the first prospective, randomised, comparative study of telbivudine-roadmap vs tenofovir-roadmap concept in HBeAg-negative patients with CHB. Both treatments based on the roadmap concept were effective over the 156 wk treatment period. Moreover, telbivudine showed an improvement in eGFR from baseline while a deterioration was observed with tenofovir; this could be an important consideration for long term therapy in CHB patients especially in those with a high risk for renal impairment.

ACKNOWLEDGMENTS

The authors acknowledge the work of the OPTIMA investigators and participating institutions located in various countries. The investigators included Peter Ferenci and Wolfgang Vogel (Austria); Rozalina Balabanska, Jordan Genov, and Krum Katarov (Bulgaria); Thomas Berg, Peter Buggisch, Heinz Hartmann, Hartwig Klinker, Jens Rasenack, Hans Wedemeyer, and Stefan Zeuzem

(Germany); Evangelos Akriviadis, Alexandra Alexopoulou, Ioannis Elefsiniotis, and Konstantinos Mimidis (Greece); Evangelista Sagnelli (Italy); Djamal Abdurakhmanov, Pavel Bogomolov, Vladimir Chulanov, Marina Maevskaya, Maria Matsievich, Igor Nikitin, Olga Znoiko, and Konstantin Zhdanov (Russia); Maria Buti Ferret, Jose Luis Calleja, Albert Pardo, and Ricard Sola Lamoglia (Spain); Ulus Akarca, Iftihar Koksai, and Fehmi Tabak (Turkey). The authors would like to thank Krassimir Antonov, Deian Jelev, Lyudmila Mateva, and Dimitar Popov (Bulgaria) for their technical assistance. Medical writing support was provided by Farid Khalfi (Novartis Ireland Ltd., Dublin, Ireland).

COMMENTS

Background

Hepatitis B virus (HBV) infection is the major cause of chronic hepatitis worldwide. Emergence of resistance due to prolonged nucleos(t)ide analogue use or incomplete suppression of HBV still remains an important concern. Therefore, early virologic response at week 24 of therapy has been used to predict better outcomes and to reduce the risk of antiviral resistance.

Research frontiers

This study used the response-guided add-on strategy (roadmap concept). For patients with HBV DNA ≥ 300 copies/mL (≥ 51 IU/mL) at week 24, tenofovir was added to telbivudine by week 26 in the telbivudine arm, and telbivudine was added to tenofovir by week 26 in the tenofovir arm. For patients with HBV DNA < 300 copies/mL at week 24, telbivudine and tenofovir monotherapies in the respective arms were continued.

Innovations and breakthroughs

This was the first prospective, randomised, 2-arm, open-label, non-inferiority study in hepatitis B e antigen (HBeAg)-negative chronic hepatitis B (CHB) patients that compared telbivudine and tenofovir administered as per the roadmap concept. The safety of the combination of telbivudine and tenofovir, for which limited data are currently available, was also evaluated.

Applications

Efficacy was shown for both telbivudine-roadmap and tenofovir-roadmap regimens in HBeAg-negative CHB patients over 156 wk. Both treatments showed acceptable safety profiles. In addition, the telbivudine arm was associated with renal improvement.

Peer-review

This is an extensive randomised study to compare the roadmap treatment strategy between telbivudine and tenofovir in patients with HBeAg-negative CHB patients. As antiviral treatment may be life-long, renal protection becomes an important consideration. The current manuscript should be of benefit to the hepatologists and liver transplantation specialists worldwide.

REFERENCES

- Schweitzer A, Horn J, Mikolajczyk RT, Krause G, Ott JJ. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. *Lancet* 2015; **386**: 1546-1555 [PMID: 26231459 DOI: 10.1016/s0140-6736(15)61412-x]
- Tang CM, Yau TO, Yu J. Management of chronic hepatitis B infection: current treatment guidelines, challenges, and new developments. *World J Gastroenterol* 2014; **20**: 6262-6278 [PMID: 24876747 DOI: 10.3748/wjg.v20.i20.6262]
- World Health Organization. Hepatitis B Fact Sheet No. 204. July 2015. Available from: URL: <http://www.who.int/mediacentre/>

- factsheets/fs204/en/
- 4 **Zoulim F**, Locarnini S. Optimal management of chronic hepatitis B patients with treatment failure and antiviral drug resistance. *Liver Int* 2013; **33** Suppl 1: 116-124 [PMID: 23286855 DOI: 10.1111/liv.12069]
- 5 **Gu EL**, Yu YQ, Wang JL, Ji YY, Ma XY, Xie Q, Pan HY, Wu SM, Li J, Chen CW, Xu XW, Wang YE, Yao GB, Wang H, Zhang WH. Response-guided treatment of cirrhotic chronic hepatitis B patients: multicenter prospective study. *World J Gastroenterol* 2015; **21**: 653-660 [PMID: 25605989 DOI: 10.3748/wjg.v21.i2.653]
- 6 **Ryu HJ**, Lee JM, Ahn SH, Kim do Y, Lee MH, Han KH, Chon CY, Park JY. Efficacy of adefovir add-on lamivudine rescue therapy compared with switching to entecavir monotherapy in patients with lamivudine-resistant chronic hepatitis B. *J Med Virol* 2010; **82**: 1835-1842 [PMID: 20872709 DOI: 10.1002/jmv.21898]
- 7 **Yang YJ**, Shim JH, Kim KM, Lim YS, Lee HC. Assessment of current criteria for primary nonresponse in chronic hepatitis B patients receiving entecavir therapy. *Hepatology* 2014; **59**: 1303-1310 [PMID: 24170683 DOI: 10.1002/hep.26910]
- 8 **Shin JW**, Jung SW, Park BR, Kim CJ, Eum JB, Kim BG, Du Jeong I, Bang SJ, Park NH. HBV DNA level at 24 weeks is the best predictor of virological response to adefovir add-on therapy in patients with lamivudine resistance. *Antivir Ther* 2012; **17**: 387-394 [PMID: 22293395 DOI: 10.3851/imp1945]
- 9 **Lo AO**, Wong GL. Current developments in nucleoside/nucleotide analogues for hepatitis B. *Expert Rev Gastroenterol Hepatol* 2014; **8**: 607-622 [PMID: 24787673 DOI: 10.1586/17474124.2014.909724]
- 10 **Gane EJ**. The Roadmap concept: using early on-treatment virologic responses to optimize long-term outcomes for patients with chronic hepatitis B. *Hepatol Int* 2008; **2**: 304-307 [PMID: 19669258 DOI: 10.1007/s12072-008-9083-0]
- 11 **Sun J**, Xie Q, Tan D, Ning Q, Niu J, Bai X, Fan R, Chen S, Cheng J, Yu Y, Wang H, Xu M, Shi G, Wan M, Chen X, Tang H, Sheng J, Dou X, Shi J, Ren H, Wang M, Zhang H, Gao Z, Chen C, Ma H, Jia J, Hou J. The 104-week efficacy and safety of telbivudine-based optimization strategy in chronic hepatitis B patients: a randomized, controlled study. *Hepatology* 2014; **59**: 1283-1292 [PMID: 24382690 DOI: 10.1002/hep.26885]
- 12 **Piratvisuth T**, Komolmit P, Tanwandee T, Sukeepaisarnjaroen W, Chan HL, Pessoa MG, Fassio E, Ono SK, Bessone F, Daruich J, Zeuzem S, Cheinquer H, Pathan R, Dong Y, Trylesinski A. 52-week efficacy and safety of telbivudine with conditional tenofovir intensification at week 24 in HBsAg-positive chronic hepatitis B. *PLoS One* 2013; **8**: e54279 [PMID: 23390496 DOI: 10.1371/journal.pone.0054279]
- 13 **Liu F**, Wang X, Wei F, Hu H, Zhang D, Hu P, Ren H. Efficacy and resistance in de novo combination lamivudine and adefovir dipivoxil therapy versus entecavir monotherapy for the treatment-naïve patients with chronic hepatitis B: a meta-analysis. *Virol J* 2014; **11**: 59 [PMID: 24673792 DOI: 10.1186/1743-422x-11-59]
- 14 **Yu HC**, Lin KH, Hsu PI, Tsay FW, Wang HM, Tsai TJ, Lai KH. Real-world application of the roadmap model in chronic hepatitis B patients with telbivudine therapy. *Clin Ther* 2013; **35**: 1386-1399 [PMID: 24054706 DOI: 10.1016/j.clinthera.2013.07.329]
- 15 **Liaw YF**, Gane E, Leung N, Zeuzem S, Wang Y, Lai CL, Heathcote EJ, Manns M, Bzowej N, Niu J, Han SH, Hwang SG, Cakaloglu Y, Tong MJ, Papatheodoridis G, Chen Y, Brown NA, Albanis E, Galil K, Naoumov NV. 2-Year GLOBE trial results: telbivudine is superior to lamivudine in patients with chronic hepatitis B. *Gastroenterology* 2009; **136**: 486-495 [PMID: 19027013 DOI: 10.1053/j.gastro.2008.10.026]
- 16 **Zeuzem S**, Gane E, Liaw YF, Lim SG, DiBisceglie A, Buti M, Chutaputti A, Rasenack J, Hou J, O'Brien C, Nguyen TT, Jia J, Poynard T, Belanger B, Bao W, Naoumov NV. Baseline characteristics and early on-treatment response predict the outcomes of 2 years of telbivudine treatment of chronic hepatitis B. *J Hepatol* 2009; **51**: 11-20 [PMID: 19345439 DOI: 10.1016/j.jhep.2008.12.019]
- 17 **Wang Y**, Thongsawat S, Gane EJ, Liaw YF, Jia J, Hou J, Chan HL, Papatheodoridis G, Wan M, Niu J, Bao W, Trylesinski A, Naoumov NV. Efficacy and safety of continuous 4-year telbivudine treatment in patients with chronic hepatitis B. *J Viral Hepat* 2013; **20**: e37-e46 [PMID: 23490388 DOI: 10.1111/jvh.12025]
- 18 **Lai CL**, Gane E, Liaw YF, Hsu CW, Thongsawat S, Wang Y, Chen Y, Heathcote EJ, Rasenack J, Bzowej N, Naoumov NV, Di Bisceglie AM, Zeuzem S, Moon YM, Goodman Z, Chao G, Constance BF, Brown NA. Telbivudine versus lamivudine in patients with chronic hepatitis B. *N Engl J Med* 2007; **357**: 2576-2588 [PMID: 18094378 DOI: 10.1056/NEJMoa066422]
- 19 **Seto WK**, Lai CL, Fung J, Wong DK, Yuen JC, Hung IF, Yuen MF. Significance of HBV DNA levels at 12 weeks of telbivudine treatment and the 3 years treatment outcome. *J Hepatol* 2011; **55**: 522-528 [PMID: 21147187 DOI: 10.1016/j.jhep.2010.11.018]
- 20 **Wang YH**, Wu BQ, Liu H. Continuous venovenous hemodiafiltration for hyperlactatemia caused by telbivudine in a patient with chronic hepatitis B: a case report and update review. *J Dig Dis* 2015; **16**: 164-167 [PMID: 25043654 DOI: 10.1111/1751-2980.12173]
- 21 **Chan HL**, Chen YC, Gane EJ, Sarin SK, Suh DJ, Piratvisuth T, Prabhakar B, Hwang SG, Choudhuri G, Safadi R, Tanwandee T, Chutaputti A, Yurdaydin C, Bao W, Avila C, Trylesinski A. Randomized clinical trial: efficacy and safety of telbivudine and lamivudine in treatment-naïve patients with HBV-related decompensated cirrhosis. *J Viral Hepat* 2012; **19**: 732-743 [PMID: 22967105 DOI: 10.1111/j.1365-2893.2012.01600.x]
- 22 **Liaw YF**, Raptopoulou-Gigi M, Cheinquer H, Sarin SK, Tanwandee T, Leung N, Peng CY, Myers RP, Brown RS, Jr., Jeffers L, Tsai N, Bialkowska J, Tang S, Beebe S, Cooney E. Efficacy and safety of entecavir versus adefovir in chronic hepatitis B patients with hepatic decompensation: a randomized, open-label study. *Hepatology* (Baltimore, Md) 2011; **54**: 91-100 [PMID: 21503940 DOI: 10.1002/hep.24361]
- 23 **Mallet V**, Schwarzsinger M, Vallet-Pichard A, Fontaine H, Corouge M, Sogni P, Pol S. Effect of nucleoside and nucleotide analogues on renal function in patients with chronic hepatitis B virus mono-infection. *Clin Gastroenterol Hepatol* 2015; **13**: 1181-1188. e1181 [PMID: 25460550 DOI: 10.1016/j.cgh.2014.11.021]
- 24 **EASL clinical practice guidelines: Management of chronic hepatitis B virus infection. J Hepatol 2012; **57**: 167-185 [PMID: 22436845 DOI: 10.1016/j.jhep.2012.02.010]**
- 25 **Qi X**, Wang JY, Mao RC, Zhang JM. Impact of nucleos(t)ide analogues on the estimated glomerular filtration rate in patients with chronic hepatitis B: a prospective cohort study in China. *J Viral Hepat* 2015; **22**: 46-54 [PMID: 25402626 DOI: 10.1111/jvh.12229]
- 26 **Gane EJ**, Deray G, Liaw YF, Lim SG, Lai CL, Rasenack J, Wang Y, Papatheodoridis G, Di Bisceglie A, Buti M, Samuel D, Uddin A, Bosset S, Trylesinski A. Telbivudine improves renal function in patients with chronic hepatitis B. *Gastroenterology* 2014; **146**: 138-146. e135 [PMID: 24067879 DOI: 10.1053/j.gastro.2013.09.031]
- 27 **Tsai MC**, Chen CH, Hung CH, Lee CM, Chiu KW, Wang JH, Lu SN, Tseng PL, Chang KC, Yen YH, Hu TH. A comparison of efficacy and safety of 2-year telbivudine and entecavir treatment in patients with chronic hepatitis B: a match-control study. *Clin Microbiol Infect* 2014; **20**: O90-O100 [PMID: 23659493 DOI: 10.1111/1469-0691.12220]
- 28 **Lee M**, Oh S, Lee HJ, Yeum TS, Lee JH, Yu SJ, Kim HY, Yoon JH, Lee HS, Kim YJ. Telbivudine protects renal function in patients with chronic hepatitis B infection in conjunction with adefovir-based combination therapy. *J Viral Hepat* 2014; **21**: 873-881 [PMID: 24351112 DOI: 10.1111/jvh.12217]
- 29 **Amarapurkar DN**, Patel N. Increased eGFR with telbivudine in combination therapy of chronic hepatitis B infection. *Indian J Gastroenterol* 2014; **33**: 89-91 [PMID: 23512213 DOI: 10.1007/s12664-013-0325-2]
- 30 **Tsai MC**, Yu HC, Hung CH, Lee CM, Chiu KW, Lin MT, Tseng PL, Chang KC, Yen YH, Chen CH, Hu TH. Comparing the efficacy and clinical outcome of telbivudine and entecavir naïve patients with hepatitis B virus-related compensated cirrhosis. *J Gastroenterol Hepatol* 2014; **29**: 568-575 [PMID: 24716215]

- 31 **Liang KH**, Chen YC, Hsu CW, Chang ML, Yeh CT. Decrease of serum Angiotensin converting enzyme levels upon telbivudine treatment for chronic hepatitis B virus infection and negative correlations between the enzyme levels and estimated glomerular filtration rates. *Hepat Mon* 2014; **14**: e15074 [PMID: 24596580 DOI: 10.5812/hepatmon.15074]

P- Reviewer: Balaban YH, Chiu KW, Cholongitas EC, Chuang QL, Gong ZJ, Montasser MF, Romero MR, Wong GLH, Zhu Z
S- Editor: Qiu S **L- Editor:** A **E- Editor:** Li D





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: bpgoffice@wjgnet.com

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>

