Title

104-week efficacy and safety of telbivudine based optimization strategy in chronic hepatitis B patients: A randomized, controlled study

Jian Sun¹, Qing Xie², Deming Tan³, Qin Ning⁴, Junqi Niu⁵, Xuefan Bai⁶, Rong Fan¹, Shijun Chen⁷, Jun Cheng⁸, Yanyan Yu⁹, Hao Wang¹⁰, Min Xu¹¹, Guangfeng Shi¹², Mobin Wan¹³, Xinyue Chen¹⁴, Hong Tang¹⁵, Jifang Sheng¹⁶, Xiaoguang Dou¹⁷, Junping Shi¹⁸, Hong Ren¹⁹, Maorong Wang²⁰, Hongfei Zhang²¹, Zhiliang Gao²², Chengwei Chen²³, Hong Ma²⁴, Jidong Jia²⁴, Jinlin Hou¹

Affiliations:

¹Hepatology Unit, Nanfang Hospital, Southern Medical University, Guangzhou;
²Department of Infectious Diseases, Ruijin Hospital, Shanghai;
³Department of Infectious Diseases, Xiangya Hospital, Central South University, Changsha;
⁴Department and Institute of Infectious Disease, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan;
⁵Hepatology Unit, No. 1 Hospital affiliated to Jilin University, Changchun;
⁶Department of Infectious Diseases, Tangdu Hospital, Xi'an;
⁷Jinan Infectious Diseases Hospital, Jinan;
⁸Beijing Ditan Hospital, Beijing;
⁹Department of Infectious Diseases, First Hospital of Peking University, Beijing;
¹⁰Hepatology Unit, Peking University People’s Hospital, Beijing;
¹¹8th People's Hospital, Guangzhou;
¹²Department of Infectious Diseases, Huashan Hospital, Fudan University, Shanghai;

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/hep.26885
13 Department of Infectious Diseases, Shanghai Hospital, Shanghai;
14 Beijing Youan Hospital, Beijing;
15 Department of Infectious Diseases, West China Hospital, Chengdu;
16 Department of Infectious Diseases, Zhejiang University 1st Affiliated Hospital, Hangzhou;
17 Department of Infectious Diseases, Shengjing Hospital of China Medical University, Shenyang;
18 6th People's Hospital, Hangzhou;
19 Department of Infectious Diseases, The second Affiliated Hospital, Chongqing Medical University, Chongqing;
20 Department of Infectious Diseases, 81st PLA Hospital, Nanjing;
21 302nd PLA Hospital, Beijing;
22 Department of Infectious Diseases, Sun Yat-Sen University 3rd Affiliated Hospital, Guangzhou;
23 Department of Infectious Diseases, 85th PLA Hospital, Shanghai;
24 Liver Research Center, Beijing Friendship Hospital, Capital Medical University, Beijing, China.

Contact Information:

Jian Sun Email: doctorsunjian@qq.com
Qing Xie Email: xieqingrj@gmail.com
Deming Tan Email: dmt2008@aliyun.com
Qin Ning Email: qning@vip.sina.com
Junqi Niu Email: junqiniu@yahoo.com.cn
Keywords:

Hepatitis B e antigen positive, ROADMAP concept, virological response, adefovir, suboptimal responder
Correspondence:

Jinlin Hou

Hepatology Unit, Nanfang Hospital, Southern Medical University

Guangzhou, 510515

China

Tel: 00862061641941

Fax: 00862087719653

Email: jlhousmu@163.com

List of Abbreviations:

HBV: Hepatitis B virus; CHB: chronic hepatitis B; ALT: alanine aminotransferase; ULN: the upper limit of normal; LLOD: the lower limit of detection; IFN: interferon; NUC: nucleos(t)ide analogues; ITT: intention to treat; eGFR: estimated glomerular filtration rate; MDRD: Modification of Diet in Renal Disease; PCR: polymerase chain reaction; LOCF: the last observation carried forward; SAE: serious adverse event; HBsAg: hepatitis B surface antigen; HBsAb, hepatitis B surface antibody; HBeAg, hepatitis B e antigen; HBeAb, hepatitis B e antibody.

Financial Support:

This study was funded by National Science and Technology Major Project (2012ZX10002003).

Conflicts of interest

QN has been a member of Advisory Committees or Review Panels, received consulting fees from Roche, Novartis, GlaxoSmithKline, Bristol-Myers Squibb and has received
grant/research support from Roche, Novartis and Bristol-Myers Squibb. XGD has sat on advisory boards for Roche, Bristol-Myers Squibb, Merck Sharp & Dohme, GSK, and Novartis and received honoraria as a speaker for Roche, Merck Sharp & Dohme, Bristol-Myers Squibb, GSK, and Novartis. HM has received research grants from Roche, Novartis, Bristol-Myers Squibb and GSK; and received honoraria as a speaker for Roche, Novartis and Sanofi-Aventis.

JDJ has acted as a consultant for Novartis, Bristol-Myers Squibb, GSK, Roche and Merck Sharp & Dohme. JLH has received consulting fees from Roche, Novartis, GSK, Bristol-Myers Squibb and has received grant/research support from Roche, Novartis and GSK. The other authors declare that they have no conflicts of interest.

Author contribution:

JLH, JDJ, JS were involved in the study design. JS, QX, DMT, QN, JQN, XFB, RF, SJC, JC, YYYY, HW, MX, GFS, MBW, XYC, HT, JFS, XGD, JPS, HR, MRW, HFZ, ZLG, CWC, HM collected data. JLH, JS and RF analysed and interpreted the data and wrote the manuscript.

JLH approved the final manuscript. All authors had full access to the final version of the report and agreed to the submission.
Abstract

Optimization strategy based on ROADMAP concept is supposed to improve the clinical outcomes of patients with suboptimal antiviral response. The aim of this study is to prove the concept with a multicenter, open-label, randomized, controlled study. Six hundred and six Hepatitis B e antigen (HBeAg) -positive, nucleos(t)ide-naive chronic hepatitis B patients were randomized to OPTIMIZE or MONO group. Patients in OPTIMIZE group were treated with telbivudine for 24 weeks, after which those suboptimal responders with HBV DNA ≥ 300 copies/mL at week 24 received telbivudine plus adefovir until week 104, while the early virological responders continued telbivudine monotherapy. Patients in MONO group received telbivudine monotherapy. All patients with telbivudine monotherapy were added on adefovir if viral breakthrough developed. Sixty eight percent (204/300) patients in OPTIMIZE group were added on adefovir due to suboptimal response. At week 104, compared to MONO group, more patients in OPTIMIZE group achieved HBV DNA < 300 copies/ml (76.7% vs. 61.2%, p<0.001) with less genotypic resistance (2.7% vs. 25.8%, p<0.001). The rates of HBeAg seroconversion and ALT normalization were comparable between two groups (23.7% vs. 22.1%; 80.7% vs. 79.2%). For week 24 suboptimal responders, telbivudine plus adefovir showed additive antiviral potency with 71.1% achieving virological response at week 104 and only 0.5% developing genotypic resistance, compared with 46.6% who achieved virological response and 37.8% who developed genotypic resistance with telbivudine monotherapy. Both treatment regimens were well tolerated with observed persistent increase of glomerular filtration rate. **Conclusion:** For suboptimal virological responders to telbivudine at week 24, adjusting treatment strategy is recommended. Adding on adefovir can benefit these patients.
with additive antiviral potency and low resistance without increased side effect.
Introduction

Hepatitis B virus (HBV) affects more than 350 million people worldwide and is responsible for more than 1 million deaths from end-stage liver diseases annually.\textsuperscript{1, 2} About 75\% of them reside in the Asia-Pacific region.\textsuperscript{3} Hence, more efforts should be made in this area to efficiently manage the disease with antiviral therapy, which will contribute significantly to a better control of worldwide HBV infection.

Several oral antiviral agents have been approved for chronic hepatitis B (CHB) treatment, with both entecavir and tenofovir being recommended as first-line therapy by major international guidelines.\textsuperscript{4-6} However, due to economic issues and tenofovir not being approved for CHB in some counties, majority of Asian-Pacific CHB patients have obstacles to receive first-line therapy. Therefore, low genetic barrier drugs are still extensively used,\textsuperscript{7} especially in countries where generic lamivudine and adefovir are available, resulting in high chance of suboptimal response and resistance. To better manage the antiviral treatment using the low genetic barrier drugs in the Asia-Pacific region, exploratory studies are needed to optimize treatment in these patients with suboptimal response.

In 2007, a panel of hepatologists proposed the “ROADMAP concept”, in which patients with suboptimal response after 24-weeks of treatment with the initial drug will either switch to a more potent agent or add on a second agent without cross-resistance to the initial drug.\textsuperscript{8} Although some pilot studies have shown that the optimization strategy worked well in real world or clinical trials with limited sample size,\textsuperscript{9-14} the ROADMAP concept has not been confirmed in any prospective, well-controlled, randomized study with sufficient sample size.
The “ROADMAP concept” was derived primarily from phase III global registration study of telbivudine, results of which demonstrated that telbivudine is superior to lamivudine.\textsuperscript{15} As the data for adefovir applying “ROADMAP concept” is limited, we conducted the EFFicacy Optimization of Response to Telbivudine (EFFORT) study, with the objective to evaluate the efficacy and safety of ROADMAP strategy by adding adefovir to telbivudine for suboptimal responders, and comparing their response to that of patient treated with telbivudine monotherapy in nucleos(t)ide-naive patients with HBeAg positive CHB. Here, we report the final 2-year efficacy and safety results from this trial.

**Methods**

**Study design**

This multicentre, open-label, randomized, controlled, 2-year study (NCT00962533) was conducted at 24 centers in China from August 2009 to March 2012. Eligible patients were randomized at a 1:1 ratio to telbivudine-based optimized group (OPTIMIZE) or telbivudine monotherapy group (MONO). Patients in OPTIMIZE group started telbivudine 600 mg daily, and adefovir 10 mg daily was added to patients with suboptimal response (24-week HBV DNA \(\geq 300\) copies/mL) from week 28 to week 104 (OPTIMIZE-combo subgroup); patients with early virological response (24-week HBV DNA <300 copies/mL at week 24) continued telbivudine monotherapy until week 104 (OPTIMIZE-mono subgroup). Patients in MONO group received telbivudine monotherapy from baseline until week 104. All patients with telbivudine monotherapy were added on adefovir as rescue treatment once confirmed virological breakthrough developed (Figure 1).
At randomization, stratified and permuted-block randomization (mixed block size of 4 and 6) was performed. Stratification factors included baseline HBV DNA levels ($\leq 9 \log_{10}$ or $> 9 \log_{10}$ copies/mL) and alanine aminotransferase (ALT) levels ($\leq 5$ or $> 5$ times the upper limit of normal (ULN)). The distribution of randomization code was performed by PAREXEL International using fax machine.

Clinical, laboratory, and adverse event assessments were done every 12 or 16 weeks from baseline to week 104. HBV DNA level and HBV serological markers were measured with the platform of Roche COBAS Taqman (with the lower limit of detection (LLOD) of 12 IU/mL or 69.84 copies/mL) and ARCHITECT i2000SR at the central laboratory set up by the research group; a result lower than LLOD was replaced by LLOD when appropriate. Serum ALT levels were assessed at local laboratories according to standard procedures.

This study was conducted in compliance with the ethics principles of the Declaration of Helsinki and Good Clinical Practice and China regulatory requirements. The study protocol was approved by ethics committee at each participating center. Written informed consent was obtained from all screened patients.

**Patients**

Patients aged 18-65 years were eligible if Hepatitis B surface antigen (HBsAg) positive for at least 6 months, HBeAg positive and hepatitis B e antibody (HBeAb) negative, HBV DNA $> 5 \log_{10}$ copies/mL (4.24 log$_{10}$ IU/mL), ALT $\geq 2$ and $< 10 \times$ ULN (determined on two occasions at least 14 days apart within 6 months before randomization). Patients who had received previous treatment with interferon (IFN) within one year, or nucleos(t)ide analogues (NUC) at
any time were excluded. Additional exclusion criteria included other forms of liver disease; evidence of hepatic decompensation, pancreatitis, or hepatocellular carcinoma; co-infection with hepatitis C, hepatitis D, or the human immunodeficiency virus; presence of telbivudine/adeovir-related resistance mutations (i.e. M204I/V, N236T or A181V/T); serum creatinine level >1.5 mg/dL; serum amylase >1.5 × ULN; prothrombin time prolonged by >3 sec; serum albumin level <3.5 g/dL; and bilirubin level >2.0 mg/dL. Eligible patients with serum alpha fetoprotein level >50 ng/mL required exclusion of underlying HCC.

**Efficacy and Safety Endpoints**

Efficacy analyses included all randomized patients who received at least one dose of study medication and underwent at least one HBV DNA assessment after baseline (intention to treat [ITT] population). The primary efficacy endpoint was the proportion of patients with virological response, defined as HBV DNA <300 copies/mL (52 IU/mL) at week 104. Secondary efficacy endpoints at week 104 included HBV DNA reduction from baseline and the proportions of patients with ALT normalization, HBeAg loss, HBeAg seroconversion (HBeAg loss with detectable hepatitis B e antibody [HBeAb]), HBsAg loss, HBsAg seroconversion (HBsAg loss with detectable hepatitis B surface antibody [HBsAb]), virological breakthrough and genotypic resistance.

Safety analyses included all patients who underwent randomization and received at least one dose of study medication and had at least one safety assessment after the baseline assessment. Assessment of safety included serious and non-serious adverse events, and graded laboratory abnormalities. Estimated glomerular filtration rate (eGFR) was calculated by
Virological Breakthrough and Resistance

Virological breakthrough was defined as an increase of HBV DNA by $\geq 1 \log_{10}$ above nadir on two consecutive occasions at least one month apart after achieving an initial response in a compliant patient.\(^5\) Patients who experienced virological breakthrough at the time of withdrawing the study (including at week 104) without confirmation value one month later, were conservatively treated as virological breakthrough. Genotypic resistance was defined as virological breakthrough with treatment-emergent genotypic resistance mutations (M204I, A181V/T and N236T).\(^15,17\) HBV DNA was amplified by polymerase chain reaction (PCR) from serum samples at screening for all patients and at the time points of confirmed virological breakthrough.

Statistical analysis

The chi-square test with continuity corrected approach was used to calculate the sample size (nQuery Advisor v7.0). The sample size of 285 per arm was calculated to detect a difference in virological response rate (HBV DNA $< 300$ copies/mL) of 72% in OPTIMIZE group versus 60% in MONO group at week 104, with a two-sided significance level of 5% and power of 83%. The sample size was increased to 300 patients per arm to allow for 5% of dropout rate.

According to the published paper,\(^18\) for HBeAg positive chronic hepatitis B patients treated with telbivudine monotherapy with baseline ALT $\geq 2 \times$ULN, 61% of them achieved HBV DNA $< 300$ copies/mL at week 104. So the virological response rate of MONO group at week 104 was set as 60%. For OPTIMIZE group, it is expected that 55% patients will need to add...
on adefovir due to suboptimal response. For these patients, after adding on adefovir, we assumed that the rate of HBV DNA <300 copies/mL at week 104 could be increased from 40% to 60%. Based on the assumption, for the overall population in OPTIMIZE group, we assumed that 72% patients could achieve HBV DNA < 300 copies/mL at week 104.

For analyses of dichotomous endpoints, missing values were considered as failures, and the chi-square or Fisher’s exact test were used to compare differences in the treatment groups. For analyses of continuous variables, the last observation carried forward (LOCF) method was used to handle missing values. Analysis was planned for subgroup of patients with early virological response and suboptimal response. All reported p values are two-sided. All analyses were done with SAS version 9.2. An interim analysis was performed when all patients completed 52 weeks of treatment.

Results

Patient population

Of the 606 patients who were randomized, 599 patients were included in the efficacy analyses (intention-to-treat [ITT] population), with 300 in OPTIMIZE group and 299 in MONO group. Seven patients were excluded from the ITT population (2 patients did not receive study drug and 5 patients had no HBV DNA assessment after baseline).

The most common reasons for treatment discontinuation were patient’s request (OPTIMIZE, 7; MONO, 11), non-compliance (OPTIMIZE, 2; MONO, 4) and adverse events (OPTIMIZE, 4; MONO, 2). At the end of the study, 282 (94.0%) and 278 (93.0%) patients completed the 104-week treatment respectively (Figure 2). Treatment groups were well balanced at baseline
with respect to demographics and other characteristics, with 38.7% genotype B and 60.8% genotype C in both groups. The mean baseline HBV DNA level was $8.49 \log_{10}$ copies/mL with mean ALT level of $4.31 \times ULN$ overall in both groups (Table 1).

**Efficacy in the overall population**

**Virological Response**

Patients in OPTIMIZE group achieved better viral control than those in MONO group. The difference in HBV DNA $< 300$ copies/mL was significant by week 36 and continued to increase through week 104 (Figure 3). More patients in OPTIMIZE group achieved virological response than those in MONO group at week 52 (65.3% vs. 56.9%, $p=0.033$) and week 104 (76.7% vs. 61.2%, $p<0.001$, Table 2). In addition, at week 104, serum HBV DNA reduction from baseline was significantly greater in OPTIMIZE group ($6.3 \log_{10}$) than MONO group ($6.1 \log_{10}$; $P<0.001$).

**Biochemical and Serologic Response**

Among patients with abnormal ALT (ALT $>1 \times ULN$) at baseline, 80.7% of patients in OPTIMIZE group achieved normalization of ALT compared with 79.2% of patients in MONO group at week 104 ($p=0.649$). Comparable proportions of patients in the OPTIMIZE and MONO groups achieved HBeAg loss (29.0% vs. 31.1%, $p=0.574$) and HBeAg seroconversion (23.7% vs. 22.1%, $p=0.643$). HBsAg loss (0.7% vs. 0.7%) and HBsAg seroconversion (0.3% vs. 0.3%) were rare in both treatment groups (Table 2). All 4 patients with HBsAg loss had baseline HBV DNA $< 9 \log_{10}$ copies/mL ($8.24 \log_{10}$ IU/mL), and 3 of them achieved HBV DNA $<300$ copies/ml at week 24. Among 137 patients with HBeAg
séroconversion at week 104, 133 (97.1%) achieved HBV DNA <300 copies/mL at week 104.

**Virological Breakthrough and Resistance**

The rates of virological breakthrough and genotypic resistance in OPTIMIZE group were significantly lower compared to those in MONO group by week 52 (1.0% vs. 7.7%, p <0.001 for virological breakthrough; 0.7% vs. 7.0%, p<0.001 for resistance) and week 104 (6.0% vs. 30.4%, p <0.001 for virological breakthrough; 2.7% vs. 25.8%, p<0.001 for resistance) (Table 2).

The signature mutation associated with telbivudine resistance was rtM204I (84/85). Unexpectedly, there was a single case of telbivudine resistance with rtM204V (1/85) with secondary mutation of rtL180M. The adefovir-related mutations (rtN236T, rtA181V/T) were not found in patients with virological breakthrough by week 104 in either group. The first case of virological breakthrough occurred at week 41 during telbivudine monotherapy. Majority of virological breakthrough and resistance occurred between weeks 52 and 104 (Figure 4).

**Efficacy in subgroups**

We further regrouped the overall population according to the assigned treatment strategy (OPTIMIZE or MONO) and 24-week virological response (suboptimal or early responder).

**Analyses of suboptimal responders**

Adefovir was added for 204/300 patients (68.0%) in OPTIMIZE group due to suboptimal response defined as 24-week HBV DNA ≥300 copies/mL (OPTIMIZE-combo subgroup), while 193 patients (64.5%) with suboptimal response in MONO group continued on
telbivudine monotherapy. The efficacy between these two subgroups was compared to show the benefit of adding on adefovir for suboptimal responders.

Among OPTIMIZE-combo subgroup of patients, 71.1% (145/204) achieved virological response at week 104, compared with 46.6% (90/193) in MONO subgroup. Only one case of resistance was found in OPTIMIZE-combo subgroup with corresponding resistance rate of 0.5% (1/204). In contrast, a total of 73/193 (37.8%) patients developed resistance in MONO subgroup with telbivudine monotherapy. The proportion of patients with HBeAg seroconversion was comparable between these two subgroups (14.7% vs. 12.4%) (Figure 5).

One of the major advantages of adding on adefovir is reduction of genotypic resistance. In order to compare antiviral potency of telbivudine versus telbivudine plus adefovir in suboptimal responders, we excluded patients who developed genotypic resistance in both subgroups and analysed their treatment response. The results still showed that significantly more patients achieved virological response at week 104 in OPTIMIZE-combo subgroup (71.4% vs. 56.7%, p=0.007). These results also suggest that for suboptimal responders, telbivudine plus adefovir have additive antiviral potency compared with telbivudine monotherapy.

**Analyses of early responders**

Among the ITT population (N=599), 201 patients (33.6%) achieved early response (HBV DNA <300 copies/mL) at week 24 and continued telbivudine monotherapy. For these early responders, 88.6% patients maintained virological response and 41.3% achieved HBeAg seroconversion at week 104. However, 5.5% developed genotypic resistance. For early
responders who achieved HBeAg seroconversion, only one patient developed genotypic resistance by week 104.

Safety

The safety profile observed in this study was in line with that in the previous telbivudine phase III study. Among safety population, both telbivudine monotherapy and the combination of telbivudine with adefovir were well tolerated. Adverse events were reported in nearly 40% of patients in both treatment arms (Table 3) and most adverse events were not attributed to study drug by the clinical investigators. Blood creatine kinase increase was reported in 15.7% and 14.7% of patients in OPTIMIZE and MONO groups, and was the most frequently reported event, followed by nasopharyngitis (5.3% and 4.3%) and upper respiratory tract infection (3.7% and 4.3%). Serious adverse event (SAE), regardless of causality to study drug, were reported in 10 patients (3.3%) and 17 patients (5.7%) in OPTIMIZE and MONO groups, respectively. A total of 7 drug-related SAE were reported in the study: 2 in OPTIMIZE group (myopathy[1], peripheral neuropathy[1]) and 5 in MONO group (hepatitis flare [2], myopathy[1], myalgia[1], cardiac enzymes increased[1]). Six of these events resolved without sequelae, and 1 event (peripheral neuropathy) improved. Two patients were diagnosed with hepatocellular carcinoma and were not considered to be related to study drug, one of them died after hepatectomy. Myopathy was reported in 3 patients (2 in OPTIMIZE, 1 in MONO). Around 8% patients had Grade 3-4 creatine kinase elevation; however, most of them were transient (98% lasted for only 1 visit; 2% lasted for 2 visits) and did not translate into musculoskeletal side effects (88% without muscle events reported). In addition, telbivudine therapy was associated with consistent increase of eGFR from baseline.
in patients receiving either telbivudine (+12.4 mL/min/1.73 m²) or telbivudine plus adefovir (+13.2 mL/min/1.73 m²). Patients with impaired renal function at baseline showed greater eGFR improvement after 104 weeks of treatment compared to the overall population. The changes in eGFR levels from baseline (in patients with baseline eGFR <90 mL/min/1.73 m²) were +25.1 mL/min/1.73 m² with telbivudine monotherapy and +14.4 mL/min/1.73 m² with telbivudine plus adefovir treatment.

**Discussion**

International CHB clinical practice guidelines have recognized the high rate of suboptimal response and resistance with the use of low genetic barrier drugs. European clinical practice guideline recommend that patients who have a partial virological response at week 24 while receiving lamivudine or telbivudine should switch to a more potent drug or add on a drug without cross-resistance, namely ROADMAP concept. These recommendations are based on expert opinion and retrospective analysis which needed to be supported by further study.

This study is the first randomized, controlled and concept proving study, to show the efficacy and safety of optimization strategy with adding on non-cross-resistant drugs for suboptimal responders at week 24 based on the ROADMAP concept.

Based on results from this study, the application of optimization strategy has successfully improved the 104-week virological response by 25.3% and decreased the resistance rate by 89.5%, compared to monotherapy. For those suboptimal responders who continued telbivudine monotherapy after week 24 in MONO group, only 46.6% of them achieved virological response and as high as 37.8% developed resistance at week 104. These prospective results are
in line with retrospective analysis of telbivudine registration study, which showed that for patients not achieving early virological response, around 39.3% patients developed resistance at year 2. In contrast, for suboptimal responders who were treated with adefovir plus telbivudine combination therapy, 71.1% achieved virological response at week 104 after adding on adefovir at week 28. Of these, only 0.5% patients developed resistance. To further prove the additive potency of telbivudine plus adefovir combination therapy for suboptimal responders, we excluded those patients with genotypic resistance and compared the virological response between telbivudine monotherapy and telbivudine plus adefovir in these patients. This analysis still showed improved virological response in the combination group. This further proved that for suboptimal responders, adding on adefovir does not only prevent resistance, but also increase antiviral potency. This solid evidence supported the EASL and APASL guidelines that modification of treatment strategy is recommended and adding on adefovir is effective for suboptimal responders at week 24 in patients treated with telbivudine.

Improved viral control after addition of adefovir did not translate into higher serological response. For suboptimal responders at week 24, HBeAg seroconversion rates are comparable between telbivudine monotherapy and telbivudine plus adefovir combination therapy at week 104 (14.7% vs. 12.4%). However, for early virological responders at week 24, 41.3% achieved HBeAg seroconversion at week 104, this response is approximately three fold higher than that observed in suboptimal responders. In addition, all patients with HBeAg seroconversion achieved HBV DNA <300 copies/mL before seroconversion developed. This highlights the importance of achieving early and complete viral suppression before the development of
serological response. For high genetic barrier drugs, to our knowledge, no data have reported the relationship between early virological suppression and serological response. In addition, the strong potency did not translate into higher serological response compared with low genetic barrier drugs.\textsuperscript{21-23}

Achieving serological response is also an important goal of anti-HBV treatment, especially for young patients in the Asia-Pacific region.\textsuperscript{4} Identification of early virological responders is helpful in order to shorten treatment duration. For patients achieving HBeAg seroconversion, only 1 patient developed genotypic resistance by week 104, suggesting that over 40% of patients with early virological response could achieve HBeAg seroconversion without resistance within 2 years. Such an approach would make treatment discontinuation possible for these patients based on current guidelines.

As 10 mg adefovir is not the ideal dosage for viral suppression, intensification with tenofovir may achieve even better results. A recent study by Piratvisuth et al. showed very promising results in suboptimal responders treated with tenofovir and telbivudine combination therapy. In that study, 93% patients achieved virological response at week 52 without virological breakthrough in the overall population.\textsuperscript{9} However, as tenofovir has not been approved for the treatment of CHB in some Asian countries, adefovir was the best available choice for us to optimize treatment response to telbivudine. Furthermore, adefovir is also more cost-effective in China, making it more practical. In addition, switching to entecavir may be another choice. A study from Hong Kong recommended to switch from telbivudine to entecavir at month 6-12 among incomplete responders to telbivudine if the HBV DNA is <2000 IU/ml at the time of switching.\textsuperscript{11}
Telbivudine monotherapy or combination with adefovir were well tolerated during the 104-week treatment, consistent with previous clinical findings,\textsuperscript{15, 18, 19} thus suggesting a satisfactory safety profile for telbivudine and adefovir combination therapy. Creatine kinase elevations were still frequent with telbivudine-based treatment, and drug-related myopathy events were uncommon. eGFR increase was observed during the telbivudine based therapy, especially in patients with mild renal insufficiency, reflecting the possible renal sparing effect of telbivudine.

Although the optimization strategy proved to be successful in improving treatment outcome in this study, there are still some concerns or questions over this strategy. First, to what extent will this strategy change the clinical practice of CHB? As long-term treatment with oral nucleos(t)ides is usually needed, an antiviral agent with low resistance is preferred. Both AASLD and EASL guidelines only recommend entecavir and tenofovir as first line therapy for treatment naive patients, not recommending telbivudine or adefovir as first line choice.\textsuperscript{4, 6}

Although the overall virological response in the optimization group is not inferior to entecavir or tenofovir monotherapy for HBeAg positive patients, the overall resistance rate is still higher than that seen with entecavir or tenofovir, especially taking into consideration the restricted population (virological breakthrough) for genotypic resistance analysis in this study, which may underestimate the resistance rate.\textsuperscript{21, 24} In addition, the long-term resistance rate of the optimization strategy is still being investigated in the extension study. Second, as around two thirds of patients in the optimized group were treated with combination therapy, cost-effectiveness is another concern. As drug prices are different across different regions, previous cost-effective analysis with the ROADMAP strategy from Europe and Asia reached
conflicting results.\textsuperscript{25,26} Adefovir, especially generic adefovir, is the cheapest antiviral drug in China, followed by lamivudine and telbivudine. Considering not all patients have easy access to entecavir and tenofovir, telbivudine-based optimization strategy is a promising solution in the real world situation in this area. Taken together, it is difficult to challenge the first line recommendation of entecavir and tenofovir for treatment naive CHB patients. However, for patients who have been treated with low genetic barriers drugs, optimization strategy based on the ROADMAP concept is strongly preferred over monotherapy.

In conclusion, the current study showed that the optimization strategy with adefovir add-on in patients without early virological response after 24 weeks of telbivudine treatment significantly improved efficacy outcomes with favourable safety profile at 2 years. The combination of adefovir and telbivudine, based on the ROADMAP strategy, is a promising strategy in Asia-Pacific region to optimize antiviral treatment outcome in CHB patients.
References


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Figure legends

**Figure 1.** EFFORT study design. Patients in OPTIMIZE group started telbivudine 600 mg daily from baseline, and adefovir 10 mg daily was added to patients with suboptimal response (week 24 HBV DNA ≥300 copies/mL) from week 28 (OPTIMIZE-combo); patients with early response (week 24 HBV DNA <300 copies/mL at week 24) continued telbivudine monotherapy (OPTIMIZE-mono). Patients in MONO group started telbivudine monotherapy from baseline to week 104. All patients with telbivudine monotherapy were added on adefovir once confirmed virological breakthrough developed.

**Figure 2** EFFORT study flowchart.

**Figure 3** Virological Response (HBV DNA <300 copies/mL) from baseline to week 104 (Missing = Failure).

**Figure 4.** Cumulative incidences of virological breakthrough (A) and genotypic resistance (B) by week 104.

**Figure 5.** Efficacy at week 104 in suboptimal responders (HBV DNA ≥300 copies/mL at week 24) with telbivudine monotherapy versus adefovir plus telbivudine: Virological response, HBeAg seroconversion, genotypic resistance (Missing = Failure).
Table 1  Demographic and Baseline Characteristics of the Patients*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>OPTIMIZE group (N=300)</th>
<th>MONO group (N=299)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Years of age—mean (range)</strong></td>
<td>29 (18, 61)</td>
<td>31 (18, 63)</td>
</tr>
<tr>
<td><strong>Male sex—n (%)</strong></td>
<td>245 (81.7%)</td>
<td>243 (81.3%)</td>
</tr>
<tr>
<td><strong>HBV genotype—no. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>122 (40.7%)</td>
<td>110 (37%)</td>
</tr>
<tr>
<td>C</td>
<td>177 (59%)</td>
<td>187 (63%)</td>
</tr>
<tr>
<td>Others</td>
<td>1 (0.3%)</td>
<td>2 (0.7%)</td>
</tr>
<tr>
<td><strong>Serum ALT level—ULN</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>4.3±3.7</td>
<td>4.3±3.8</td>
</tr>
<tr>
<td>Median (range)</td>
<td>2.9 (0.5, 22.7)</td>
<td>3.3 (0.2, 43.4)</td>
</tr>
<tr>
<td><strong>Serum HBV DNA level—log_{10} copies/ml</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>8.4±1.1</td>
<td>8.6±1.0</td>
</tr>
<tr>
<td>Median (range)</td>
<td>8.7 (3.8, 10.6)</td>
<td>8.8 (4.6, 10.4)</td>
</tr>
<tr>
<td><strong>Serum HBsAg level—log_{10} IU/ml</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>4.2±0.7</td>
<td>4.3±0.6</td>
</tr>
<tr>
<td>Median (range)</td>
<td>4.3 (1.6, 5.4)</td>
<td>4.3 (2.3, 5.6)</td>
</tr>
<tr>
<td><strong>Serum HBeAg level—log_{10} PEIU/ml</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>2.6±0.9</td>
<td>2.7±0.9</td>
</tr>
<tr>
<td>Median (range)</td>
<td>2.9 (-0.6, 4.2)</td>
<td>3.0 (-0.6, 4.0)</td>
</tr>
</tbody>
</table>

* All subjects were HBsAg positive, HBeAg positive and Chinese patients. ALT=alanine aminotransferase; ULN = upper limit of normal; HBsAg = hepatitis B surface antigen; HBeAg = hepatitis B e antigen.
Table 2  Efficacy Results at Week 52 and Week 104

<table>
<thead>
<tr>
<th>Variables</th>
<th>Week 52</th>
<th>Week 104</th>
<th>P value</th>
<th>Week 52</th>
<th>Week 104</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OPTIMIZE (N=300)</td>
<td>MONO (N=299)</td>
<td>P value</td>
<td>OPTIMIZE (N=300)</td>
<td>MONO (N=299)</td>
<td>P value</td>
</tr>
<tr>
<td>Virological response (%)*</td>
<td>65.3 (196/300)</td>
<td>56.9 (170/299)</td>
<td>0.033</td>
<td>76.7 (230/300)</td>
<td>61.2 (183/299)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum HBV DNA (median change in ( \log_{10} ) copies/ml from baseline)</td>
<td>-6.0</td>
<td>-5.8</td>
<td>0.048</td>
<td>-6.3</td>
<td>-6.1</td>
<td>0.009</td>
</tr>
<tr>
<td>ALT normalization (%)†</td>
<td>80.7 (234/290)</td>
<td>88.7 (260/293)</td>
<td>0.007</td>
<td>80.7 (234/290)</td>
<td>79.2 (232/293)</td>
<td>0.649</td>
</tr>
<tr>
<td>HBeAg loss (%)</td>
<td>16.7 (50/300)</td>
<td>20.7 (62/299)</td>
<td>0.202</td>
<td>29.0 (87/300)</td>
<td>31.1 (93/299)</td>
<td>0.574</td>
</tr>
<tr>
<td>HBeAg seroconversion (%)</td>
<td>14.3 (43/300)</td>
<td>17.4 (52/299)</td>
<td>0.306</td>
<td>23.7 (71/300)</td>
<td>22.1 (66/299)</td>
<td>0.643</td>
</tr>
<tr>
<td>HBsAg loss (%)</td>
<td>0</td>
<td>0.3 (1/299)</td>
<td>0.499</td>
<td>0.7 (2/300)</td>
<td>0.7 (2/299)</td>
<td>1.000</td>
</tr>
<tr>
<td>HBsAg seroconversion (%)</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>0.3 (1/300)</td>
<td>0.3 (1/299)</td>
<td>1.000</td>
</tr>
<tr>
<td>Virological Breakthrough (%)‡</td>
<td>1.0 (3/300)</td>
<td>7.7 (23/299)</td>
<td>&lt;0.001</td>
<td>6.0 (18/300)</td>
<td>30.4 (91/299)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Genotypic Resistance (%)‡</td>
<td>0.7 (2/300)</td>
<td>7.0 (21/299)</td>
<td>&lt;0.001</td>
<td>2.7 (8/300)</td>
<td>25.8 (77/299)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

NOTE. For categorical end points, missing values were considered as failure. For continuous end points, the missing values were analyzed by LOCF method. CI, confidence interval.
* Virological response was defined as serum HBV DNA <300 copies/ml.

† Calculated for patients with serum ALT >1 times the ULN at baseline (n=291 and 297 in OPTIMISE group and MONO group, respectively).

‡ Virological Breakthrough was defined as an increase of HBV DNA by ≥1 Log above nadir on two consecutive occasions at least one month apart after achieving an initial response in a compliant patient. Those patients who experienced virological breakthrough at the time of withdrawing this study (including at week 104) without confirmation value one month later, were conservatively treated as virological breakthrough. Genotypic Resistance was defined as virological breakthrough with identified treatment-emergent resistance mutations.
### Table 3  Summary of cumulative safety data

<table>
<thead>
<tr>
<th>Outcomes at week 104</th>
<th>OPTIMISE (N=300)</th>
<th>MONO (N=300)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Most frequent adverse events (≥2%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any adverse event (%)</td>
<td>37.3</td>
<td>39.0</td>
</tr>
<tr>
<td>Blood creatine phosphokinase increased (%)</td>
<td>15.7</td>
<td>14.7</td>
</tr>
<tr>
<td>Nasopharyngitis (%)</td>
<td>5.3</td>
<td>4.3</td>
</tr>
<tr>
<td>Upper respiratory tract infection (%)</td>
<td>3.7</td>
<td>4.3</td>
</tr>
<tr>
<td>Myalgia (%)</td>
<td>2.3</td>
<td>2.3</td>
</tr>
<tr>
<td>Fatigue (%)</td>
<td>3.3</td>
<td>1.7</td>
</tr>
<tr>
<td>Decreased appetite (%)</td>
<td>2.0</td>
<td>1.3</td>
</tr>
<tr>
<td><strong>Serious adverse event (%)</strong></td>
<td>3.3</td>
<td>5.7</td>
</tr>
<tr>
<td><strong>Death (%)</strong></td>
<td>0.3</td>
<td>0</td>
</tr>
<tr>
<td><strong>Grades 3/4 laboratory abnormalities (%)†</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatine kinase</td>
<td>8.3</td>
<td>9.7</td>
</tr>
<tr>
<td>Alanine aminotransferase</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>Aspartate aminotransferase</td>
<td>0</td>
<td>0.3</td>
</tr>
<tr>
<td>Amylase</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* The patient’s death was the outcome of an SAE of hepatocellular carcinoma and was considered to be not related to study drug.

† Patients are counted only once in each row. The severity of laboratory abnormalities was graded according to criteria adapted from the Division of AIDS, National Institute of Allergy and Infectious Diseases. Grades 3/4 elevations in aminotransferase levels are those >5 times baseline; Grades 3/4 elevations in creatine kinase levels are those at least 7 times the upper limit of normal; Grades 3/4 elevations in Amylase are those at least 5 times the upper limit of normal.
EFFORT study design. Patients in OPTIMIZE group started telbivudine 600 mg daily from baseline, and adefovir 10 mg daily was added to patients with suboptimal response (week 24 HBV DNA ≥300 copies/mL) from week 28 (OPTIMIZE-combo); patients with early response (week 24 HBV DNA <300 copies/mL at week 24) continued telbivudine monotherapy (OPTIMIZE-mono). Patients in MONO group started telbivudine monotherapy from baseline to week 104. All patients with telbivudine monotherapy were added on adefovir once confirmed virological breakthrough developed.
EFFORT study flowchart.

210x220mm (300 x 300 DPI)
Virological Response (HBV DNA <300 copies/mL) from baseline to week 104 (Missing = Failure).

220x151mm (300 x 300 DPI)
Cumulative incidences of virological breakthrough (A) and genotypic resistance (B) by week 104.
Efficacy at week 104 in suboptimal responders (HBV DNA ≥300 copies/mL at week 24) with telbivudine monotherapy versus adefovir plus telbivudine: Virological response, HBeAg seroconversion, genotypic resistance (Missing = Failure).

192x132mm (300 x 300 DPI)
Acknowledgments

Parts of this study were presented at the Asian Pacific Association for the Study of the Liver (APASL) Liver Week 2013, Jun 6-9, Singapore; 22nd Conference of the Asian Pacific Association for the Study of the Liver (APASL 2012), February 16-19, Taipei, Taiwan and the 46th annual meeting of the European Association for the Study of the Liver (EASL 2012), April 18-24, Barcelona, Spain. We thank the study investigators, coordinators, nurses, patients and their families for their contributions. We also wish to thank Prof Hui Zhuang from Peking University health science center, Aldo Trylesinski, Yuhong Dong and Lena Shapiro from Novartis Pharma AG, Basel for their helpful assistance on the data analysis and language polish. PAREXEL International provided professional monitoring, data management and statistical analysis. Abbott Diagnostics provided partly free kits for HBV serological test and HBeAg Paul-Ehrlich international (PEI) reference standard. Novartis provided free study drug and financially supported monitoring service.