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RESPONSES TO REVIEWERS

Name of Journal: *World Journal of Hepatology*

ESPS Manuscript NO: 25600

Manuscript Type: Randomized Clinical Trial

Telbivudine versus tenofovir in HBeAg-negative chronic hepatitis B patients: OPTIMA roadmap study

1- Reviewer's code: 03384301:

Comments to Authors

1-The paper is well written with good English language 2- This manuscript announces that this was the first prospective, randomised, non-inferiority study in HBeAg-negative CHB patients that compared telbivudine and tenofovir administered as per roadmap concept. I have some queries : 1- Method of measurement of HBv DNA through the different centers involved in the study was it central lab recruitment or local lab in each center? the method of standardization and the machine use this should be clear in the methods as one of the difficulties in HBV treatment and follow up is the falicies in HBV DNA measurements. 2- In the Patient demographics and clinical characteristics (A total of 241 patients (121 in the telbivudine arm and 120 in the tenofovir arm) were randomised in this study.A total of 20 (16.5%) patients in the telbivudine arm and 11 (9.2%) patients in the tenofovir arm discontinued prematurely from the study. The most common reasons for discontinuation in the telbivudine arm were consent withdrawal (n=6), lost to follow-up (n=5) and administrative reasons (n=4). In the tenofovir arm, the most common reasons for discontinuation were AEs (n=4) and lost to follow-up (n=4). What was the AE in theremaining 5

patients in telbivudine arm and 3 patients in Tenofovir arm? 3- the authors mentioned (A total of 113 (93.4%) patients in the telbivudine arm and 117 (97.5%) patients in the tenofovir arm comprised the rITT population and were includedin the primary efficacy analysis. The per-protocol population consisted of 103 (85.1%) patients in the telbivudine arm and 113 (94.2%) patients in the tenofovir arm. The safety population comprised 120 patients in each of the 2 arms. One patient in the telbivudine arm was excluded from the safety population as this patient did not receive any study treatment.) The numbers need to be more clarified is it on 113 patients or 103 in telbivudine arm and the Tenofovir arm also. In addition i suggest a study design chart to simplify this issue including the discontinuations number, the patients with Ae, and the rITT.

Responses

1- 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, USA).

This sentence was added in the "materials and methods" section.

2- The other reasons for discontinuation in the telbivudine arm were AE (n=2), protocol deviation (n=2) and abnormal test procedure result (n=1). In the tenofovir arm, the other reasons for discontinuation were consent withdrawal (n=2) and protocol deviation (n=1).

We have kept in the manuscript the most common reasons.

3- The authors acknowledge the reviewer's comment. We have summarized the analysed populations and included in the manuscript the following text:

The safety population comprised 120 patients in each of the telbivudine and tenofovir 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 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 103 (85.1%) patients in the telbivudine arm and 113 (94.2%) patients in the tenofovir arm. A total of 19 patients (14 in the telbivudine arm and 5 in the tenofovir arm) were excluded from the per-protocol population because of major protocol deviations.

Considering this added summary and the 6 figures already within the manuscript, the authors believe that adding a new figure is not necessary.

2- Reviewer's code: 00761439:

Comments to Authors

This is a very interesting and well written randomized trial regarding the administration of telbivudine vs tenofovir in 241 HBeAg negative chronic hepatitis B patients. The authors concluded that both treatments based on the roadmap concept were effective over the 104-week treatment period. Moreover, telbivudine showed an improvement in eGFR from baseline. There are few issues which should be addressed by the authors 1) In Table 1: variables without normal distribution should be presented as median (range) 2) Can the authors provide more data regarding which adverse events were significantly different between the two arms? 3) Improvement of GFR was observed in those with telbivudine plus tenofovir or only in those under telbivudine monotherapy? 4) In conclusions, the authors should add that tenofovir was added more frequently in telbivudine arm.

Responses

1-Medians (ranges) have been provided in Table 1.

2- Increased blood CPK levels (in 27 (22.5%) patients) and nausea (in 7 (5.8%) patients) were the drug-related AEs that were observed more frequently in the telbivudine arm compared to the tenofovir arm (15 (12.5%) patients and 2 (1.7%) patients, respectively).

This sentence was added in the "safety" section.

3- Telbivudine monotherapy was associated with a significant improvement in eGFR as compared with tenofovir monotherapy.

This is mentioned in the "safety" section.

4- A higher proportion of patients in the telbivudine arm required add on therapy (22 patients at Week 24 and an additional 12 patients post Week 24; 34/121 overall) than in the tenofovir arm (11/120).

This is mentioned in the "efficacy" section.

3- Reviewer's code: 02444774:

Comments to Authors

This was a pharma-sponosred RCT of non-inferiority design to compare telbivudine and tenofovir administered as per roadmap concept. The sample size was respectable. Major comments: 1. The sample size estimation was 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. The 10% non-inferiority margin might be too generous. 2. I cannot understand why TDF arm needed add-on telbivudine, as the resistance rate was so low and patients would have increased chance of undetectable HBV DNA with time. 3. What were the explanations on exceptionally low week 104 HBV DNA undetectable rate? The rate in TDF arm was as low as 74.4%, which was even lower than keeping TDF monotherapy without adding LdT. 4. Using virological endpoint at two years may not be sufficient. With time probably more patients in the LdT arm need add-on so making this strategy not as appealing.

Responses

1- A -10% non-inferiority margin was used following the completed pivotal global registration studies for both telbivudine (Lai et al 2007) and entecavir (Lai et al 2006).

- Lai CL, Gane E, Liaw YF, Hsu CW, Thongsawat S, Wang Y, et al. Telbivudine versus lamivudine in patients with chronic hepatitis B. N Engl J Med 2007; 357: 2576-88.
- Lai CL, Shouval D, Lok AS, Chang TT, Cheinquer H, Goodman Z, et al. Entecavir versus lamivudine for patients with HBeAg-negative chronic hepatitis B. N Engl J Med 2006; 354: 1011-20.

2- The primary objective of the study was to compare the efficacy of roadmap-concept-based telbivudine treatment versus roadmap-concept-based tenofovir treatment in HBeAg negative CHB patients. Therefore for the statistical analysis, we used the roadmap intent-to-treat population that 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).

3- The authors acknowledge the reviewer's point. We reported the results of the study. Therefore, further studies are needed to evaluate this point.

4- Our study was the first prospective, randomised clinical trial using the roadmap concept in HBeAg-negative CHB patients evaluating efficacy endpoints at 1 and 2 years. Therefore, further studies are needed to determine whether long-term telbivudine treatment needs add-on therapy.

4- Reviewer's code: 02444986:

Comments to Authors

Comments: ? 1- If this is a "non-inferiority study", why there is a combination treatment group. Otherwise, statistical analysis should be done on 3 groups (telbivudine monotherapy, tenofovir monotherapy and combination treatment)? 2- 24 weeks is too early to add on another NA in HBe antigen negative patients. ? 3- There is no data on previous antiviral treatment of patients, except that they were not treated within 6 mounts previous to randomization? 4- There is no data on fibrosis scores of patients, although it is stated that all patients had liver biopsy within 12 months? 5- There is too much dropout from the study, although both NA have very well established safety profile. ? 6- There is no approval or participation of the pharmaceutical company for telbivudine (Novartis).

Responses

1- The statistical analysis using 3 groups was not chosen as the primary objective of this study was to demonstrate the non-inferiority in antiviral efficacy of telbivudine arm applying the roadmap concept compared to tenofovir arm applying the roadmap concept in adults with HBeAg-negative compensated CHB as measured by the proportion of patients (response rate)

achieving HBV DNA < 300 copies/mL after 52 weeks of treatment. Therefore, non-inferiority was used to demonstrate that telbivudine-roadmap was non-inferior to tenofovir-roadmap with a 95% CI.

2- Regarding the add-on therapy at 24 weeks, we followed the recommendations of a group of experts who proposed a roadmap concept for antiviral therapy based on early on-treatment response (Keeffe et al 2007; Zeuzem et al 2009). The panel recommended that patients with full HBV DNA suppression at 24 weeks continue the same antiviral agent. For patients with a partial response to antiviral therapy, they recommended to add another NA with a different resistance profile. Moreover, our study was the first prospective, randomised clinical trial using the roadmap concept in HBeAg-negative CHB patients. As found in the literature, undetectable HBV DNA at 24 weeks was the best predictor of clinical and virological efficacy, independent of HBeAg status (Shin et al 2012).

- Keeffe EB, Zeuzem S, Koff RS, Dieterich DT, Esteban-Mur R, Gane EJ, et al. Report of an international workshop: Roadmap for management of patients receiving oral therapy for chronic hepatitis B. Clin Gastroenterol Hepatol 2007; 5: 890-7.
- 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. Journal of hepatology 2009; 51(1): 11-20
- 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(2): 387-394.

3- There is no data on previous antiviral treatments for patients included in this study. Patients with any nucleos(t)ide or interferon/immunomodulator treatment in the previous 6 months were excluded from the study.

The last sentence is mentioned in the “materials and methods” section (exclusion criteria).

4- There is no data on fibrosis scores for patients included in this study. Patients were included in the study if liver histology report within 12 months before screening with diagnosis of chronic hepatitis B was available. Liver biopsies were not performed during this study.

This is mentioned in the "materials and methods" section (inclusion criteria).

5- The authors acknowledge the reviewer's comment. We reported the results of the study.

6- Novartis has registered the trial at ClinicalTrials.gov ID: NCT01379508. 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.

This is mentioned in the "materials and methods" section

5- Reviewer's code: 02445121:

Comments to Authors

This paper is a randomized clinical trial, which investigated the efficacy and safety comparison of telbivudine-roadmap and tenofovir-roadmap in hepatitis B e antigen (HBeAg)-negative chronic hepatitis B (CHB) patients. This was the first prospective, randomised, non-inferiority study in HBeAg-negative CHB patients that compared telbivudine and tenofovir administered as per roadmap concept. Both treatments based on the roadmap approach were effective over a 104-week treatment period. Non-inferiority of telbivudine arm to tenofovir arm was demonstrated at Week 52, with over 92% of patients in each treatment arm achieving HBV DNA level <300 copies/mL. Both treaments showed a good safety profile. Moreover, telbivudine showed an improvement in eGFR from baseline. This is a well conducted study. The experiments are described in detail, the results are impressive. This study is suggested for publishing in the journal.

Responses

The authors would like to thank the reviewer for his/her thorough review and highly appreciate his/her approval for publication.

6- Reviewer's code: 00051373:

Comments to Authors

This is an extensive randomized study to compare the road-map treatment strategy between telbivudine and tenofovir on HBeAg(-) chronic B hepatitis patients. As we know, antiviral treatment may be a life-long treatment until the present of HBsAb. Therefore, the renal protection is one of the majority strategies for the chronic B hepatitis patients not only, but also the hepatitis B related recipients underwent liver transplantation. The current manuscript should be benefit feedback to the hepatologists and liver transplantation center worldwide.

Responses

The authors would like to thank the reviewer for his/her thorough review and highly appreciate his/her comments.

7- Reviewer's code: 01562153:

Comments to Authors

In this manuscript, the authors evaluated the efficacy and safety comparison of telbivudine-roadmap and tenofovir-roadmap in hepatitis B e antigen (HBeAg)-negative chronic hepatitis B (CHB) patients. They found that over 92% of patients in each treatment arm achieved HBV DNA level <300 copies/mL at Week 52, that both arms were similar in key secondary efficacy variables, e.g. the percentage of patients achieving HBV DNA <300 copies/mL, ALT normalization, and the safety profile, and that telbivudine arm showed an eGFR improvement. This was a prospective, randomized clinical trial. The data were appropriately presented and interpreted. The manuscript was well prepared. Although the originality of this manuscript is not high enough, the article may provide useful information to the clinicians in managing patients with chronic hepatitis B.

Responses

The authors would like to thank the reviewer for his/her thorough review and his/her valuable comments.

8- Reviewer's code: 02444960:

Comments to Authors

This manuscript describes the roadmap concept utilizing add-on therapy comparing efficacy and safety of telbivudine with tenofovir, which could be useful in clinical practice, as a predictable tool for achieving optimal efficacy with a low emergence of drug resistance. The methodology is appropriate and the results are consistent with discussion and conclusions. This manuscript is of interest to be published on World Journal of Hepatology.

Responses

The authors would like to thank the reviewer for his/her thorough review and highly appreciate his/her approval for publication.

9- Reviewer's code: 00069297:

Comments to Authors

The authors provided some important information to manage the HBV infected patients. The manuscript was well prepared and written.

Responses

The authors would like to thank the reviewer for his/her thorough review and for the kind words.