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Review Article

The Chronic Hepatitis B Treatment Virologic Response to HAART among HBV/ HIV Co-Infected Patients who Failed Lamivudine Containing Regimens

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1. Abstract

1.1. Objective

All HIV/HBV co-infected patients in Serbia have been treated with HAART containing an anti-HBV drug, irrespective of CD4 cell count and HBV disease status in order to prevent more active liver disease. Like in many developing countries, lamivudine containing HAART was used in all HBV/HIV co-infected individuals

1.2. Methods

A cross sectional cohort study was conducted to analyse the optimal treatment response of both HIV and HBV among HBV/HIV co-infected patients who underwent lamivudine containing HART, and if experienced lamivudine failure, switched to tenofovir based HAART.

1.3. Results

After the mean duration of lamivudine containing HAART of 7.3±3.2 years (range 1-15 years), lamivudine failure was recorded in 35/67 patients (52.2%). Out of twenty-two remaining subjects with favourable virologic response to lamivudine, all achieved HBs Ag loss, out of whom 2 patients developed anti-HBs antibodies, after 4.1±3.1 years (range 1-15 years), and 9±2.8 years (7-15), respectively. After additional 2.1±1.1 years of tenofovir containing HAART, hepatitis B viral load was 1.3±1.1 $\log_{10}$ IU/mL HBV DNA. After TDF introduction, the probability of achieving optimal treatment response, which included either suppression of HBV DNA to less than 20 IU/ml, and/or HBs Ag loss, was 20%, 60% and 90% after additional 2, 3 and 5 years of TDF containing HAART, respectively.

1.4. Conclusion

The outcome of tenofovir containing HAART among HBV/HIV co-infected patients, who previously failed HBV therapy with lamivudine containing HAART, suggesting that a prolonged treatment with TDF containing HAART is mandatory among those with suboptimal virologic suppression, with small risk of anti-HIV HAART failure.

2. Keywords: HIV; HBV; Co-infection; Treatment response; lamivudine; Tenofovir

3. Introduction

Chronic hepatitis B (CHB) is associated with considerably morbidity and mortality, in HIV co-infected patients [1-4]. The prevalence of HBV co-infection among HIV infected patients in Serbia is 5.6%. All HIV/HBV co-infected patients in Serbia have been treated with HAART containing an anti-HBV drug, irrespective of CD4 cell count and HBV disease status in order to prevent more active liver disease. Like in many developing countries, lamivudine containing HAART was used in all HBV/HIV co-infected individuals [5]. The main goals of antiviral therapy were to normalize the alanine amino transferase (ALT) serum activity and HBe and HBs Ag loss, preferably followed by HBe and HBs seroconversion. Sometimes later, in early 2000s, a new therapy monitoring tool, quantitative HBV DNA testing became available and HBV DNA PCR was introduced in the everyday clinical practice. Ever since, tenofovir, which became available in 2010, has been introduced in patients who failed lamivudine therapy. The main goal of TDF containing HAART was to achieve and maintain durable suppression of viral replication and hepatic inflammation. Since 2008 the European, American and most of the guidelines from developed countries, recommend tenofovir in combination with lamivudine (3TC) or emtricitabine (FTC) as the first line nucleotide/ nucleoside analogs combination treatment for HBV in the context of HIV co-infection [6, 7]. The third drug to compose HAART was a non-nucleoside reverse transcriptase inhibitor or a boosted protease inhibitor, according to most of the guidelines. This selection of the first line treatment was based on safety and efficacy of the drugs and risk of resistance. However, in Serbia lamivudine was the only antiviral drug available for the treatment of HBV infection since 2010. Therefore, lamivudine containing HAART was initiated in all HBV/ HIV co-infected patients, which was switched to a combination with tenofovir, after HBV developed resistance to lamivudine. If HIV was still susceptible to lamivudine, the drug remained in HAART.

The aim of this cross sectional cohort study was to analyze the treatment response among HBV/HIV co-infected patients who underwent HART, in terms of the optimal treatment response of both HIV and HBV.

3.1. Patients and Methods

This cohort study conducted in the University Hospital for Infectious and Tropical Diseases in Belgrade, included HIV infected patients with chronic hepatitis B, receiving HAART from January 2000 until death or December 2015. Patients with HCV co- infection were excluded from the study.

3.2. CHB Diagnosis and Therapy Monitoring

The diagnosis of chronic hepatitis B was established according to clinical presentation, biochemical and virological markers of infection, along with pathohistological finding at aspiration liver biopsy. The aspiration liver biopsy was performed in order to assess severity of fibrosis and necro inflammatory activity, which was determined using Ishak modification for hepatic activity index. In some patients, the liver biopsy was not performed due to liver failure, presence of hemangiomas or other reasons (patients' reluctance to undergo the procedure). The diagnosis of cirrhosis was established on the basis of histological, or as a combination of clinical, endoscopic and laboratory findings.

The HBV infection status was assessed using commercial immunoassays for different serological markers, such as HBsAg/Ab, HBeAg/Ab and HBcAb, according to the manufacturer's protocol. To detects and quantify HBV DNA, real time PCR (Cobas TaqMan HBV Test version 2.0, Roche Molecular Systems, Branchburg, NJ, USA),) was used. All HBV DNA values are reported in IU/ ml.For the presentation of HBV-DNA levels logarithmic scale was used. HBsAg/Ab serology was performed every six months, for all lamivudine treated patients in order to asses treatment response, precisely to timely switch patients to tenofovir after they fail lamivudine containing HAART Plasma HBVDNA levels were determined prior to the introduction of tenofovir therapy and during the course of this therapy in order to assess treatment response. This response to therapy was considered favourable in those patients who achieved and maintained undetectable viremia, or less than 20 IU of HBV DNA/ml, by a sensitive PCR assay. The achievement of this low level viremia seems important, since it will be shown that only after achieving the HBV viral load of less than 20 iu/mL (1.3 $\log_{10}$ iu/mL HBV DNA), HBs Ag loss could occur. And again, the successful therapy implies the loss of HBs and HBe antigens and even sero conversion to anti HBe anti HBs antibodies, which was shown to be possible [6]. HBV DNA sequencing was not performed for HBV resistance mutation testing.

In order to assess the progression of chronic HBV infection, serum bilirubin, ALT, prothrombin time and albumin levels were measured at the time of diagnosis, and every six months, after the introduction of antiviral therapy with lamivudine and/or tenofvir containing HAART. Antiviral therapy was introduced according to EACS recommendations.

3.3. HIV Infection Diagnosis and Therapy Monitoring

HIV infection (stages A-C) was established according to the 1998 Centers for Disease Control case definition criteria [8]. The immunological and virological responses to HAART were evaluated every 4-6 months by measuring plasma viral loads (pVL) and CD4+ T cell counts. Due to stock-outs HAART monitoring was not performed regularly at times, which led to a delay in the measurements of CD4 cell counts and viral loads. The CD4 cells were quantified by flow cytometry. Plasma HIV-1 RNA loads were measured by a quantitative real time PCR HIV RNK(Cobas TaqMan HIV Test, version 2.o, Roche Molecular Systems, Branchburg, NJ, USA), with a lower limit of detection of 20 copies/mL (1.3 $\log_{10}$). The immunological and virological responses to HAART were evaluated by plasma viral load (pVL) and CD4+ T cell count values. The following criteria for the type of response to HAART were used: the response was considered favorable in case of achievement of a sustained pVL reduction to undetectable values, along with CD4 cell count increases to above 350/μL. In contrast, treatment failure was defined as a pVL over 2.3 $\log_{10}$ copies of HIV RNA/ml of plasma regardless of immunological improvement. In addition to these two clear-cut types of response to HAART, dissociation between immunological and virological responses to HAART occurred at times, defined as achievement of undetectable viremia during treatment but without a rise in CD4 cell counts to above 350/ μL. The threshold of 350 CD4 cells/μL was taken as one precluding the mandatory HAART initiation.

Consent for participation was obtained from all, and the study was approved by the Clinical Centre of Serbia Ethics Committee.

4. Statistics

All analyses were performed using an electronic database organized in the SPSS (version 11.5) statistical package. Follow up times, serum ALT activity, CD4 cell counts, and pVL means were compared by one way ANOVA. Non-parametric variables were analyzed using Chi-square or Fisher's exact test, as appropriate. Survival rates, as well as the probabilities of diseases progression and treatment success over time, between particular subgroups, were estimated by the Kaplan-Meier survival method and compared by the log rank test. The association between successful antiviral therapy, and variables such as baseline and plasma viral loads, as well as other possibly related variables, were assessed using univariate and stepwise multivariate logistic regression models. The level of significance was 0.05.

5. Results

5.1. Baseline Characteristics

Patient population included 67 HBV/HIV co-infected individuals, out of whom 30 (44, 7%) had clinical AIDS at baseline, 13 (19.4%), had mild symptomatic HIV infection, while the remaining 24 had asymptomatic HIV infection. Their mean CD4 cell count was 233±165 cells/μL. Forty-two (62.2%) patients were late presenters, with CD4 cell count of less than 200/ μL. Regarding the CHB stage only ten patients (14.9%) had severe liver fibrosis at baseline, while 53 (79%) were HBe Ag positive, and seven patients (10.4%) each were either HBe Ag negative and HBe Ab positive, or negative for both HBe Ag and Ab. Patients were mostly young men, with the mean age of 36.1±10.3 years.

5.2. Treatment Response

5.2.1. HBV: The mean duration of lamivudine containing HAART was 7.3±3.2 years (range 1-15 years). Lamivudine failure was recorded in 35 patients (52.2%). Out of twenty-two remaining subjects with favourable virologic response to lamivudine, all achieved HBs Ag loss, out of whom 2 patients developed anti-HBs antibodies, after 4.1±3.1 years (range 1-15 years), and 9±2.8 years (7-15), respectively. All patents with successful lamivudine containing HAART remained on these regimens. The overall probability of achieving HBs Ag loss was 20%, 40% and 70%, after 3, 6 and 9 years of continual lamivudine containing HAART, respectively. At the same time in this subgroup of patients, only two subjects experienced HAART failure, with HIV viral load of 2.3 and 2.8 log10 HIV RNK cps/mL. The mean HBV viral load at the time of switching to tenofovir containing HAART was 6.2±1.5 $\log_{10}$ IU/mL HBV DNA. Regarding the level of HBV viral load prior to TDF containing HAART initiation, our patients were stratified in two subgroups, with less than 10000 IU HBV DNA/ mL, and above this value (high viremia). After additional 2.1±1.1 years of tenofovir containing HAART, hepatitis B viral load was 1.3±1.1 $\log_{10}$ IU/mL HBV DNA. This reduction was over 4x$\log_{10}$. Undetectable viremia was recorded in 12 patients, while additional 8 patients achieved HBV DNK of less than 20 IU/L at the end of the observed period, resulting in the overall rate of optimal virologic response of 55.6 %. In addition high pre-treatment viremia was a factor preventing patients to achieve optimal HBV suppression (OR 0.1 95% CI 0.03-0.9, p=0.04). The type of HIV infection response to HAART, HBe Ag status and age above 40, did not affect suppression of HBV viremia. In our series of patients the estimated HBe Ag loss was 20% after 3 years of TDF containing HAART, and rose to 30% after 4 years. However, none of our TDF treated patients achieved HBs sero conversion, while HBs Ag loss occurred in two subjects.

A Kaplan Meier analysis was used to estimate the probability of achieving and maintaining optimal treatment response, precisely HBV DNA of less than 20 IU/mL. The estimated median time to optimal treatment response was 1.6 and 3 years for HBe Ag negative, and HBe Ag positive subjects, respectively. This difference, however, was not significant (Log rank P=0.2). After TDF introduction, the probability of achieving optimal treatment response, which included either suppression of HBV DNA to less than 20 IU/ml, and/or HBs Ag loss, was 20%, 60% and 90% after additional 2, 3 and 5 years of TDF containing HAART, respectively.

5.2.2 HIV: To the end of the study period 56 (83.5%) of treated patients maintained optimal suppression of HIV replication, of which 35 (52.2%) also achieved a good immune reconstitution, while the remaining 21 (31.1%) had dissociated immunologic and virologic response to HAART. Treatment failure was registered in 11(16.4%) of treated patients. Eleven patients died during the study period, out of which 4 (4.9%), of ESLD, while others succumbed due to HIV related complications. The estimated survival of HIV/HBV co-infected individuals was 12.7 years (the probability of staying alive after 14 years was 55%).

6. Discussion

The results of our cross-sectional cohort study on HBV/HIV co-infected patients demonstrated that the use of lamivudine as the first line anti-HBV drug within HAART may be justified in settings where TDF/FTC combination is not affordable, such as in many developing countries. And still, in over one third of lamivudine containing HAART treated individuals the favourable treatment response may be achieved and maintained with long term HAART. At the same time, only two subjects from this subgroup experienced HAART failure [5]. Recently published results of a study conducted in Thailand in order to assess the long-term HBV response to lamivudine-containing HAART in HIV-HBV co-infected patients. They demonstrated that the cumulative rates of maintained HBV-DNA suppression among the patients who achieved HBV-DNA suppression were 91%, 87%, and 80% at 1, 2, and 4 years, respectively [5]. Contrary to our data, they also showed that all HBe Ag-negative patients and 63% of HBe Ag-positive HIV-HBV co-infected patients achieved long-term HBV DNA suppression while on 3TC-containing-HAART. Our HBe Ag positive and negative subjects did not have significantly different treatment response. From the beginning of the study period, up to 2008, quantitative PCR HBV DNA testing was not available, and the assessment of treatment response was performed using serum ALT activity, along with HBe and HBs Ag loss. In patents that experienced lamivudine failure for HBV and retained susceptibility of HIV to the drug, antiviral therapy was continued with TDF/ lamivudine combination with a third antiretroviral drug. With this treatment continued for additional mean 2.1 years over 50% of them achieved optimal anti-HBV treatment response, along with over 83% of HIV virologicaly suppressed subjects. In the subgroup with suboptimal anti HBV treatment response the HBV viral load was 2.4±0.8 $\log_{10}$ IU/mL HBV DNA. However, this low level viremia seems important, since only after achieving the HBV viral load of less than 20 IU/mL (1.3 $\log_{10}$ IU/mL HBV DNA), HBs Ag loss ensued [9]. Investigated the incidence and risk factors for incomplete HBV DNA suppression in HIV/HBV-co-infected patients initiating TDF based therapy and showed that incomplete suppression was associated with higher baseline HBV DNA and detectable HIV viremia at one year [9]. This is in concordance with our data which also documented that viremia over 100000 IU/ml HBV was associated with incomplete viral suppression [10]. Published a meta-analysis of available data from 23 studies which included 550 HBV/HIV-co-infected patients treated with TDF. The overall proportion achieving suppression of HBV replication was 57.4%, 79.0% and 85.6% at 1, 2 and 3 years, respectively, regardless of prior or concomitant 3TC or FTC [10]. In another open-label study of tenofovir in HIV-1 and Hepatitis B virus co-infected individuals, conducted by [11], a significant decrease in HBV DNA viral load ($4 \times \log_{10}$) was demonstrated, while 25% of treated patients underwent HBe antigen sero conversion during the one year [11]. A multi centric study conducted in Zambia and South Africa which compared 3TC and TDF containing HAART after one year of treatment of HBV/HIV co-infection documented HBs Ag loss in 20% (4/20) of lamivudine-treated and 18% (3/17) of tenofovir-treated participants (P = 0.3), while viral suppression (HBV-DNA < 20 IU/mL) was achieved in 61.5% (16/26) of lamivudine-treated and 71.4% (15/21) of tenofovir-treated participants (P = 0.477) [12]. Our data documented that after TDF introduction, the probability of achieving optimal treatment response, which included either suppression of HBV DNA to less than 20 IU/ ml, and/or HBs Ag loss, was 20%, 60% and 90% after additional 2, 3 and 5 years of TDF containing HAART, respectively. Taken together, among lamivudine, and/or TDF containing HAART treated patients with HBV/HIV co-infection the estimated median time to achieving optimal anti-HBV treatment response was 7 years. Since no viral breakthrough occurred while on TDF, we consider that a prolonged treatment with TDF containing HAART is mandatory among those

with suboptimal virologic suppression, with small risk of anti-HIV HAART failure.

7. Conclusion

As expected, lamivudin mono therapy for CHB has been of limited success, since over a half of treated patients failed it, and switching to tenofovir containing HAART was necessary. But, still in 34.3% of lamivudine treated patients for mean 4.8 years, HBs Ag loss was achieved. The benefit of tenofovir containing HAART among HBV/HIV co-infected patients, who previously failed HBV therapy with lamivudine containing HAART, was rather modest after approximately two years of treatment, while the estimated treatment success reached 90% after 5 years suggesting that the prolonged TDF therapy is mandatory to achieve the favourable response.

8. Acknowledgement

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