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Assessment of effectiveness of Tenofovir and entecavir for the treatment of nucleos (t) ide-naïve patients with chronic Hepatitis B

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Abstract
Hepatitis B is a potentially life-threatening liver infection caused by the hepatitis B virus (HBV). It is a major global health problem. It can cause chronic infection and puts people at high risk of death from cirrhosis and liver cancer. Hence the study was planned to evaluate the efficacy of tenofovir and entecavir for the treatment of nucleos (t) ide-naïve patients with chronic hepatitis B patients.
The study was planned in the 20 patients positive for the hepatitis B surface antigens and aged 20 -70 years old. The study was conducted in the Department of Pharmacology in ANMCH Gaya. The patients were receiving the tenofovir and entecavir for the treatment of nucleos (t) ide-naïve for chronic hepatitis B.
In conclusion, tenofovir is more effective than entecavir for achieving CVS in antiviral treatment (mainly with nucleoside analogues)-experienced CHB patients. Consequently, tenofovir may represent a more favourable therapeutic option with regard to durability, as well as efficacy, in these patients, while careful monitoring for the development of resistance is suggested for patients on entecavir monotherapy.

Keywords: tenofovir, entecavir, chronic hepatitis B, nucleos(t)ide-naïve

Introduction
Hepatitis B is a potentially life-threatening liver infection caused by the hepatitis B virus (HBV). It is a major global health problem. It can cause chronic infection and puts people at high risk of death from cirrhosis and liver cancer.
The hepatitis B virus can survive outside the body for at least 7 days. During this time, the virus can still cause infection if it enters the body of a person who is not protected by the vaccine. The incubation period of the hepatitis B virus is 75 days on average, but can vary from 30 to 180 days. The virus may be detected within 30 to 60 days after infection and can persist and develop into chronic hepatitis B. In highly endemic areas, hepatitis B is most commonly spread from mother to child at birth (perinatal transmission), or through horizontal transmission (exposure to infected blood), especially from an infected child to an uninfected child during the first 5 years of life. The development of chronic infection is very common in infants infected from their mothers or before the age of 5 years.
Hepatitis B is also spread by percutaneous or mucosal exposure to infected blood and various body fluids, as well as through saliva, menstrual, vaginal, and seminal fluids. Sexual transmission of hepatitis B may occur, particularly in unvaccinated men who have sex with men and heterosexual persons with multiple sex partners or contact with sex workers. Infection in adulthood leads to chronic hepatitis in less than 5% of cases. Transmission of the virus may also occur through the reuse of needles and syringes either in health-care settings or among persons who inject drugs. In addition, infection can occur during medical, surgical and dental procedures, through tattooing, or through the use of razors and similar objects that are contaminated with infected blood.
Most people do not experience any symptoms during the acute infection phase. However, some people have acute illness with symptoms that last several weeks, including yellowing of the skin and eyes (jaundice), dark urine, extreme fatigue, nausea, vomiting and abdominal pain. A small subset of persons with acute hepatitis can develop acute liver failure, which can lead to death. In some people, the hepatitis B virus can also cause a chronic liver infection that can later develop into cirrhosis (a scarring of the liver) or liver cancer.
About 1% of persons living with HBV infection (2.7 million people) are also infected with HIV. Conversely, the global prevalence of HBV infection in HIV-infected persons is 7.4%. Since 2015, WHO has recommended treatment for everyone diagnosed with HIV infection, regardless of the stage of disease. Tenofovir, which is included in the treatment combinations recommended in first intention against HIV infection, is also active against HBV [1].
The aim of chronic hepatitis B (CHB) treatment is the durable suppression of hepatitis B virus (HBV) replication, with the goals of preventing cirrhosis, liver failure, and hepatocellular carcinoma (HCC) [2-3]. A long duration of nucleos(t)ide analogue (NA) therapy is usually required to achieve a sustained response. Antiviral therapy that results in rapid and maximal viral suppression and has a high genetic barrier to resistance is most likely to achieve and maintain virologic suppression during long-term use [4]. The combination of 2 or more potent NAs may provide additive or synergistic antiviral activity, which may result in faster or more profound viral suppression. In the treatment of human immunodeficiency virus infection, combination therapy is well established as superior to sequential monotherapy in terms of efficacy and prevention of drug resistance and is

the current standard of care [5]. In CHB, few studies exploring the combination of 2 NAs in treatment naïve patients have been reported to date. With the first generation NAs adefovir dipivoxil and lamivudine, 2 years of combination therapy with both agents was more effective in terms of HBV DNA suppression and alanine aminotransferase (ALT) normalization and was associated with a lower rate of resistance development than lamivudine monotherapy; however, serologic responses were comparable between the 2 treatment groups [6]. In a study with telbivudine and lamivudine, rates of HBV DNA suppression and ALT normalization after 1 year of treatment were not significantly different between the combination of both agents and telbivudine alone, and the rate of virologic breakthrough was higher with the combination therapy [7]. Among the approved NAs, entecavir (ETV) and tenofovir disoproxil fumarate (TDF) have potent antiviral activity [8] and are currently recommended as first-line monotherapies for CHB.1,2 Both drugs achieved high rates of HBV DNA suppression and ALT normalization in phase 3 studies in hepatitis B e antigen (HBeAg)-positive and in HBeAg-negative patients and showed maintenance of viral suppression in long-term studies [9]. Hence the study was planned to evaluate the efficacy of tenofovir and entecavir for the treatment of nucleos (t) ide-naïve patients with chronic hepatitis B patients.

Methodology

The study was planned in the 20 patients positive for the hepatitis B surface antigens and aged 20 -70 years old. The study was conducted in the Department of Pharmacology in ANMCH Gaya. The patients were receiving the tenofovir and entecavir for the treatment of nucleos(t)ide-naïve for chronic hepatitis B.

Hepatitis B surface antigen (HB s Ag), HB e Ag and hepatitis B e antibody (anti-HBe) were assayed with the second-generation enzyme linked immunosorbent assay. All patients underwent blood testing for liver biochemistry (ALT, AST, ALP, GGT, albumin, and bilirubin), complete blood count, prothrombin time, and renal biochemistry before commencement of therapy. Serum HBV-DNA was measured with the TaqMan polymerase chain reaction assay.

Patients were excluded from the study if they had hepatitis D virus, hepatitis C virus and HIV, hepatocellular carcinoma or comorbidities including alcoholic, autoimmune, metabolic liver disease with steatosis or steatohepatitis.

Results & Discussion

The data from the 20 patients were collected and presented as below. The demographic data for the HBeAg positive and negative were presented as below.

Table 1: Characteristics of Patient

Parameter	HBeAg-positive Cases	HBeAg-negative Cases	Total
Total No. of Cases	4	16	20
Males	2	14	16
Females	2	2	4

Table 2: Comparison of Study Groups

Parameter	Entecavir Cases	Tenofovir Cases	Total
Presence of Cirrhosis	1	2	3
Interferon Experienced	2	12	14
Naïve patients	0	7	7
ALT (IU/L)	30 -42	25-220	30 – 220
HBV DNA	2. 2 – 4.9	2.4 – 4. 6	2.2 – 4.9

Presently, many patients have been treated with several different groups of nucleos(t)ide analogues, including multiple alternating monotherapies or combination regimens. This can raise concerns in the selection of antivirals for second- or third-line therapies, because the efficacy may be compromised by prior treatment history and cross-resistance. Drug-resistant mutants selected by prior nucleos (t) ide analogues are preserved in viral covalently closed circular DNA in the liver, and might even compromise the efficacy of subsequent antivirals to which HBV has never been exposed [0]. One recent study reported that prior treatment with low-potency lamivudine considerably affected the long-term effects of entecavir, even with no evidence of genotypic resistance to lamivudine at baseline, and the degrees of decrease in viral titer during treatment and duration of complete virologic suppression before development of resistance were both impaired [11]. In addition, lamivudine resistance variants were more likely to be present in lamivudine-experienced patients following treatment discontinuation (22%) than in lamivudine -naive patients (0%) [12].

Large long-term studies have shown that the risk of developing cirrhosis and hepatocellular carcinoma is directly proportional to the serum HBVDNA level [13-14]. With the currently approved treatment options, the main goal of treatment is complete suppression of viral replication, because persistent HBV viremia is associated with development of liver cirrhosis and hepatocellular carcinoma. Furthermore, a rapid virological response after initiation of nucleos(t)ide analogue treatment is associated with lower rates of antiviral drug resistance in the long term. [15] By implication, treatments that reduce HBV-DNA may prevent progression of liver disease in patients with CHB. These results are supported by Liaw *et al.* [16], who showed that for patients with HBeAgnegative or HBeAg-positive CHB who had cirrhosis or advanced fibrosis, treatment with lamivudine slowed the progression of liver disease, presumably by suppressing viral replication and decreasing

the resultant necroinflammatory response. Among patients with HBeAg-negative and -positive CHB who had not previously been treated with a nucleoside analogue, the rates of histological improvement, virological response and normalization of ALT levels were significantly higher at 48 weeks with entecavir than with lamivudine [17-19]. In different studies, entecavir produced more rapid and significantly greater suppression of HBVDNA than adefovir in nucleoside-naive patients, but in the studies comparing with lamivudine-resistant or adefovir-resistant groups, it had limited Efficacy [15].

Conclusion

In conclusion, tenofovir is more effective than entecavir for achieving CVS in antiviral treatment (mainly with nucleoside analogues)-experienced CHB patients. Consequently, tenofovir may represent a more favourable therapeutic option with regard to durability, as well as efficacy, in these patients, while careful monitoring for the development of resistance is suggested for patients on entecavir monotherapy.

References

1. https://www.who.int/news-room/fact-sheets/detail/hepatitis-b
2. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of chronic hepatitis B. J Hepatol. 2009; 50:227-242.
3. Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. Hepatology. 2009; 50:661-662.
4. Lok AS, Zoulim F, Locarnini S, *et al.* Antiviral drug-resistant HBV: standardization of nomenclature and assays and recommendations for management. Hepatology. 2007; 46:254-265.
5. Thompson MA, Aberg JA, Cahn P, *et al.* Antiretroviral treatment of adult HIV infection: 2010 recommendations of the International AIDS Society-USA panel. JAMA. 2010; 304:321-333.
6. Sung JJ, Lai JY, Zeuzem S, *et al.* Lamivudine compared with lamivudine and adefovir dipivoxil for the treatment of HBe Agpositive chronic hepatitis B. J Hepatol. 2008; 48:728-735.
7. Lai CL, Leung N, Teo EK, *et al.* A 1-year trial of telbivudine, lamivudine, and the combination in patients with hepatitis B e antigen-positive chronic hepatitis B. Gastroenterology. 2005; 129:528-536.
8. Woo G, Tomlinson G, Nishikawa Y, *et al.* Tenofovir and entecavir are the most effective antiviral agents for chronic hepatitis B: a systematic review and Bayesian meta-analyses. Gastroenterology. 2010; 139:1218-1229.
9. Chang TT, Lai CL, Kew YS, *et al.* Entecavir treatment for up to 5 years in patients with hepatitis B e antigen-positive chronic hepatitis B. Hepatology. 2010; 51:422-430.
10. Zoulim F, Locarnini S. Management of treatment failure in chronic hepatitis B. Journal of hepatology. 2012; 56 Suppl 1:S112–22. pmid:22300461.
11. Lee JH, Cho Y, Lee DH, Lee M, Yoo JJ, Choi WM, *et al.* Prior exposure to lamivudine increases entecavir resistance risk in chronic hepatitis B Patients without detectable lamivudine resistance. Antimicrobial agents and chemotherapy. 2014; 58(3):1730-7. pmid: 2439 5227; PubMed Central PMCID: PMC3957876.
12. Margeridon-Thermet S, Svarovskaia ES, Babrzadeh F, Martin R, Liu TF, Pacold M, *et al.* Low-level persistence of drug resistance mutations in hepatitis B virus-infected subjects with a past history of Lamivudine treatment. Antimicrobial agents and chemotherapy. 2013; 57(1):343-9. pmid: 23114756; PubMed Central PMCID: PMC3535911.
13. Chen CJ, Yang HI, Su J, *et al.* Reveal HBV Study Group. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus level. JAMA. 2006; 295:65-73.
14. Iloeje UH, Yang HI, Su J, *et al.* Risk evaluation of viral load elevation and associated liver disease/cancer in HBV (The REVEAL HBV) study group. Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. Gastroenterology. 2006; 130:678-86.
15. Rejinders JGP, Pas SD, Schutten M, *et al.* Entacavir shows limited efficacy in HBeAg positive hepatitis B patients with a partial virologic response to adefovir therapy. J Hepatol. 2009; 50:674-83.
16. Liaw YF, Sung JJY, Chow WC, *et al.* Lamivudine for patients with chronic hepatitis B and advanced liver disease. N Engl J Med. 2004; 351:1521-31.
17. Ren FY, Piao DM, Piao XX. A one year trial of entecavirtreatment in patients with HBeAg positive chronic hepatitis B. World J Gastroenterol. 2007; 13:4264-7.
18. Chang TT, Gish RG, de Man R, *et al.* A comparison of entecavir and lamivudine for HBeAg positive chronic hepatitis B. N Engl J Med. 2006; 354:1001-10.
19. Lai CL, Shouval D, Lok AS, *et al.* Entecavir versus lamivudine for patients with HBeAg negative chronic hepatitis B. N Engl J Med. 2006; 354:1011-20.