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Outcomes of Patients on Antiviral Therapy for Chronic Hepatitis B in North Bengal

Utso Aich, Kingsuk Dutta**, Robert Ekka***, Triparna Bhadra**, Arnab Garai*, Debasis Chakrabarti*****

Abstract

***Background and objectives:** There is limited evidence regarding rate and extent of regression of liver fibrosis following antiviral therapy in patients with Chronic Hepatitis B (CHB). Here we want to establish the reversibility of clinical and laboratory outcomes including HBV DNA levels and FibroScan parameters within an established time frame.*

***Methods:** 150 patients with serologically proven CHB infection on uninterrupted antiviral therapy for at least 24 months, attending Hepatitis Clinic of North Bengal Medical College and Hospital, excluding patients with any evidence of cirrhosis (clinical or radiological), concomitant Hepatitis C and HIV infection, and chronic alcoholics, during a 6 months period were enrolled in an institution based, observational, ambispective study. Post-treatment outcomes with antiviral therapy were measured in terms of fibrosis markers (APRI, FIB-4 and Median stiffness by FibroScan), HBV DNA levels, HBeAg seroconversion and laboratory parameters.*

***Results:** Significant improvement was noted in terms of biochemical, serological and radiological parameters. HBV DNA was reduced from baseline mean of 343,52,823 to 938 (SD 2051) which corroborated with the regression of liver fibrosis by reduction of non-invasive parameters like APRI and FIB-4 from baseline mean of 1.06 to 0.32 and 1.74 to 0.91, respectively. Median stiffness in FibroScan was reduced from baseline mean of 6.22 kPa to 4.87 kPa. Also, all the 8 participants who were seropositive for HBeAg at baseline, had achieved seroconversion.*

***Conclusion:** Treatment with antivirals led to significant decreased risk of decompensation and cirrhosis which was corroborated with regression of liver fibrosis, achievement of viral DNA suppression and virological seroconversion.*

***Key words:** Chronic Hepatitis B, Antivirals, FibroScan, HBV DNA quantitative assay.*

Introduction

Hepatitis B virus (HBV) is a leading cause of liver-related morbidity and mortality worldwide. An estimated 254 million people are affected globally by chronic hepatitis B infection[1]. HBV accounts for roughly 1.1 million deaths per year across the globe[2]. The estimated seroprevalence of HBV infection is as high as 0.95% in India with highest prevalence among the tribal population[3]. The incidence of chronic hepatitis B (CHB) infection is 1.46% in India, with an estimated 17 million chronic carriers[4]. It accounts for 40% of Hepatocellular Carcinoma (HCC) and 20 - 30% cases of cirrhosis in India[5]. Hepatitis B infection acquired in adulthood leads to chronic hepatitis in <5% cases, whereas infection in infancy and early childhood leads to chronic hepatitis in 95% cases[6]. The algorithm-based treatment with antiviral agents has been the most significant scientific development for treatment of HBV infection. The purpose of our study was to investigate post-treatment outcomes with anti-virals in chronic hepatitis B patients in this part of the country with respect to liver enzyme normalisation, viral DNA suppression, virological seroconversion and reversibility of liver fibrosis.

Aims

1. To study effectiveness of anti-viral therapy to prevent cirrhosis and decompensation by comparing baseline clinico-laboratory parameters with those after 24 months.
2. To study suppression of HBV DNA levels and seroconversion of HBeAg in CHB-infected patients on anti-viral therapy after 24 months.
3. To study any reversal of Liver Fibrosis after 24 months.

Material and Methods

This study enrolled chronic HBV patients attending Hepatitis Clinic of North Bengal Medical College and Hospital, Darjeeling between 1st February 2022 and 30th January 2024. It was an institution based, observational, ambispective study, which enrolled 150 patients of chronic hepatitis B infection on uninterrupted antiviral therapy for

**Junior Resident, **Senior Resident, ***Assistant Professor, ****Professor, Department of Medicine, North Bengal Medical College and Hospital, Sushrutanagar, Darjeeling - 734 012, West Bengal.*
Corresponding Author: Dr Utso Aich, Junior Resident, Department of Medicine, North Bengal Medical College and Hospital, Sushrutanagar, Darjeeling - 734 012, West Bengal. Tel: 6291463049, E-mail: utsoaich9@gmail.com

at least 24 months, excluding patients with any evidence of cirrhosis (clinical or radiological), concomitant Hepatitis C and HIV infection, and alcoholic liver disease (patients with liver disease having history of significant amount of alcohol intake, i.e., more than 2 drinks per day for women and more than 3 drinks per day for men for 10 years or more (1 drink equals ~14 g of ethanol, which is 1 beer, 4 oz of wine, or 1oz of 80% spirits) and other causes (e.g., Wilson's disease, Autoimmune hepatitis etc.). Baseline data on study parameters was collected during enrolment of patients for initiation of treatment. Data after 24 months of treatment was collected during follow-up at Hepatitis clinic. HBV infection was confirmed by HBV DNA quantification assay in all patients. Cirrhosis was diagnosed by experienced radiologists in the Radiology Department, based on the results of imaging modalities such as ultrasonography (USG) and FibroScan (LOGIQ P9 GE MAKE shear wave transient elastography). Decompensation of cirrhosis was assessed using clinical parameters (CTP score) and imaging such as USG. Clinical outcomes and other laboratory parameters (i.e., complete blood count, liver function tests, INR etc.) were evaluated in all patients. AST to platelet ratio index (APRI) score and FIB-4 index, two useful non-invasive methods of assessing liver fibrosis, were also evaluated.

Table I: Liver FibroScan.

Liver Fibrosis staging	METAVIR score	Median stiffness (kPa)
Normal-Mild	F1	6.48 - 6.60
Mild-Moderate	F2	6.60 - 8.07
Moderate-Severe	F3	8.07 - 9.31
Cirrhosis	F4	>9.31

Table I shows optimal LOGIQ S8 shear wave elastography cut-off values in terms of shear wave speed (m/s) and Young's Modulus (kPa) for classifying fibrosis stage in the patient population under evaluation. Data was acquired using R3.1.9 equivalent software and the C1-6-D probe.

APRI score calculation

APRI score = {(AST level/AST ULN) x 100}/platelet count (10^9/L)

For APRI, ULN signifies the upper limit of normal for AST which was taken as 40U/L in our study. APRI score greater than 1.5 and greater than 2.0 was used for predicting significant hepatic fibrosis and cirrhosis respectively[7].

FIB-4 index calculation

FIB-4 index = {Age (yr) x AST (IU/L)}/{platelet count (10^9/L) x √ALT (IU/L)}

FIB-4 index greater than 1.45 and greater than 3.25 was used for predicting significant hepatic fibrosis and cirrhosis respectively[8].

Table II: Child-Turcotte-Pugh (CTP) Score:

Points	1	2	3
Encephalopathy	None	Minimal (grade 1 or 2)	Advanced (grade 3 or 4)
Ascites	Absent	Controlled	Refractory
Total bilirubin (mg/dL)	<2	2 - 3	>3
Albumin (g/dL)	>3.5	2.8 - 3.5	<2.8
INR	<1.7	1.7 - 2.3	>2.3

Table II shows severity of cirrhosis in terms of CTP Score.

CTP Class A: 5 - 6 points (Compensated cirrhosis)

CTP Class B: 7 - 9 points (Significantly compromised liver function)

CTP Class C: 10 - 15 points (Decompensated cirrhosis)

Treatment with antivirals

Standard treatment protocol was followed as per the NVHCP guidelines[9]:

- Non-cirrhotic: Tenofovir disoproxil fumarate (TDF) 300 mg once daily.
- Cirrhosis without decompensation: Entecavir (ETV) 0.5 mg once daily.
- Cirrhosis with decompensation: Entecavir (ETV) 1 mg once daily.
- eGFR <60mL/min/1.73 m^2, on haemodialysis: Entecavir (ETV) 0.5 mg once daily.

Statistical analyses

Variables were reported as mean ± SD. Categorical variables were compared by Chi-squared test. Continuous variables were compared by Student's t-test. Statistical analyses were performed using Jamovi 2.6.21 software, with p-value <0.05 considered statistically significant.

Results

Characteristics of patients at baseline

A total of 150 patients, ranging from 15 to 75 years of age, 77 (51.3%) patients were in the age bracket of 25 to 44 years and the mean age at diagnosis was found to be 38 (± 13.59) years. Majority of the infected people were male (72.7%) *versus* female (27.3%). 15% of patients had a definite history of IV drug abuse. 64 participants (42 male and 22 female) had identified risk factors of acquiring Hepatitis B infection at baseline. Among those, high-risk sexual behaviour was the leading risk factor among male

participants (21.4%). Presence of tattoos was the second most common risk factor in both male (19.0%) and female (18.2%) participants.

Baseline biochemical parameters were recorded as mean ALT 86.3 (± 67.5) IU/L, mean AST 71.2 (± 49.6) IU/L. Pre-treatment mean platelet count was 1,81,820 (± 75,000)/mm^3. Baseline CTP Score was 5.74 (± 1.08) with 76.7% participants in class A and 23.3% in class B. Among 150 participants, 8 were found to be seropositive for HBeAg.

Characteristics of patients after 24 months of treatment (Figs. 1, 2, 3, and 4)

Mean ALT and AST reduced to 27.99 (± 12.58) IU/L and 28.35 (± 13.46 IU/L), respectively. Mean platelet count increased to 2,23,990 (± 62,880)/mm^3. CTP score improved to 5.00 (±0.14) with all participants belonging to class A. All 8 seropositive participants had achieved virological seroconversion. Mean APRI reduced from 1.06 (± 0.59) at baseline to 0.32 (± 0.13) after 24 months of treatment. Mean FIB-4 decreased from1.74 (± 0.82) at baseline to 0.91 (± 0.32) after 24 months of treatment. Mean Median Stiffness also improved from 6.22 (± 1.08) kPa at baseline to 4.87 (± 0.76) kPa after 24 months of treatment. Mean HBV DNA level had reduced from a baseline mean of 343,52,823 ± (1.02E + 8) IU/mL to 938 (± 2051) IU/mL after 24 months of treatment.

Discussion

Van Ameijden *et al* reported that the HBV prevalence in Amsterdam, Netherlands, was 68% for IDUs (Injection drug users)[10]. Quite interestingly, only 12.5% of patients (6 male and 2 female) had a definite history of IV drug abuse in our study. Whereas in South Asian (including India) context, Puri has attributed the lower prevalence of CHB to the predominant horizontal transmission in early childhood, in contrast to vertical transmission seen in South-East Asia[11]. This points to the fact that other modes of transmission in adults like unsafe injection practices, occupational exposure, repeated use of same razor for multiple people

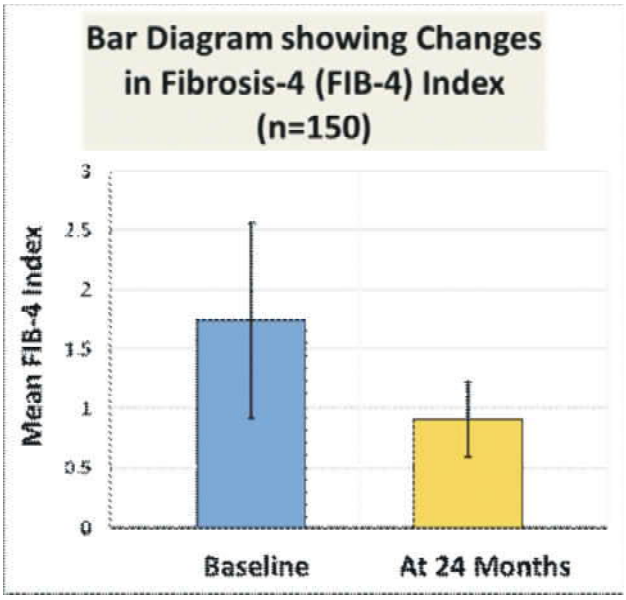

Fig. 2: *Comparison of FIB-4 index at baseline and after 24 months of treatment.*

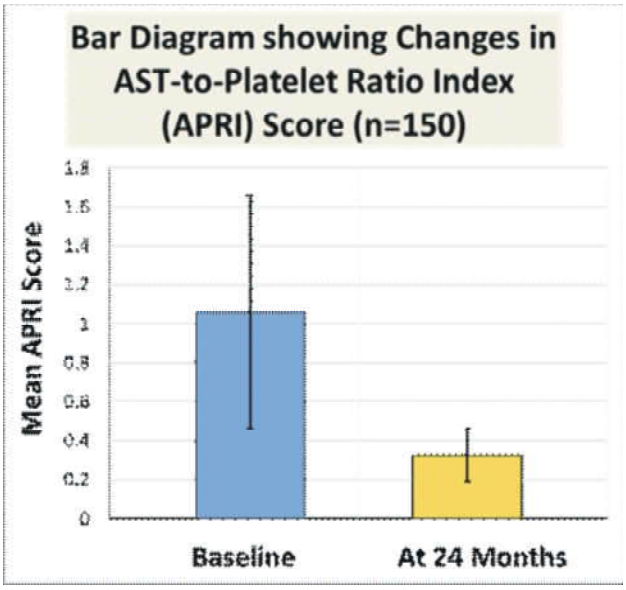

Fig.1: *Comparison of APRI score at baseline and after 24 months of treatment.*

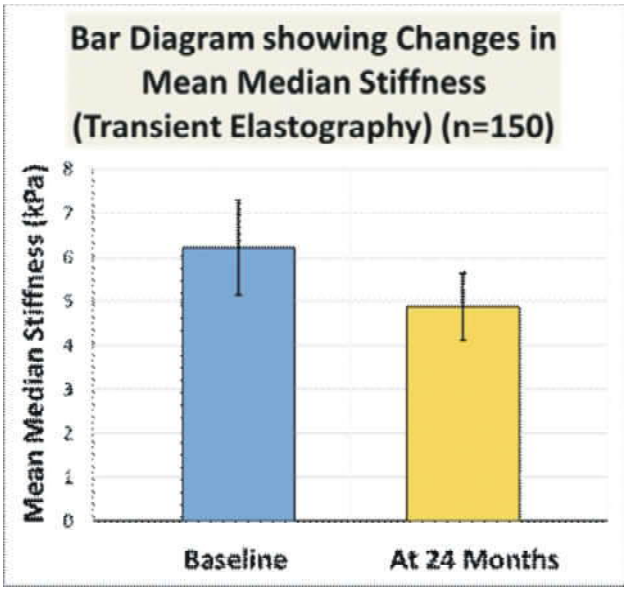

Fig. 3: *Comparison of Median Stiffness at baseline and after 24 months of treatment.*

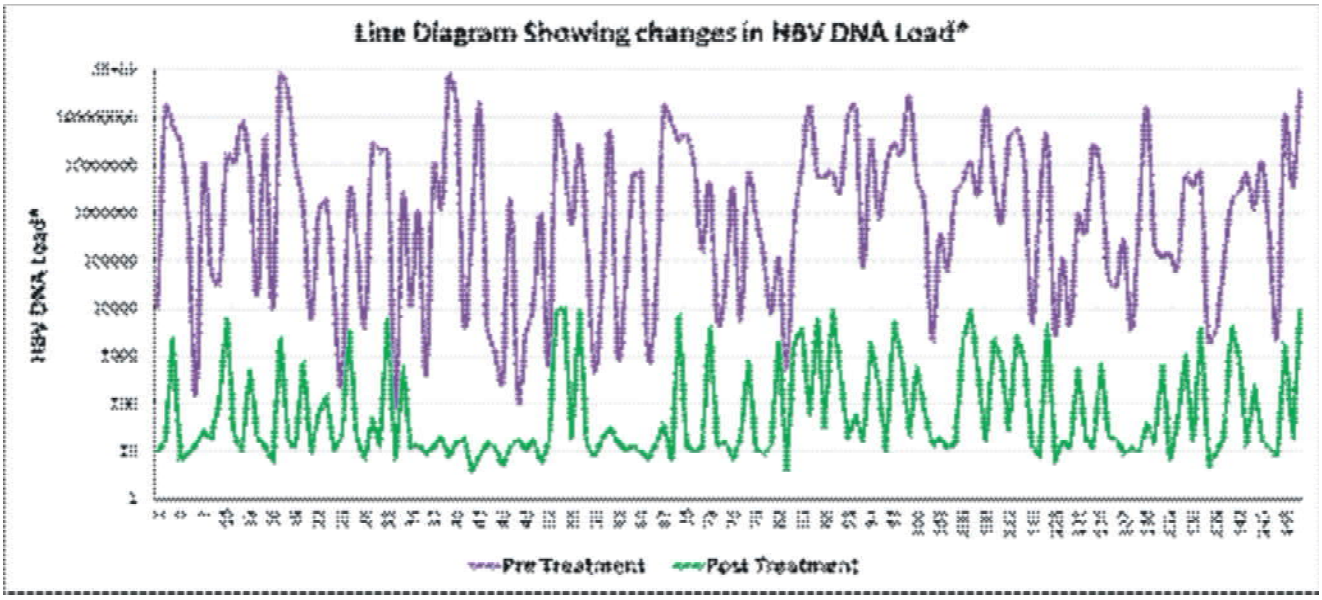

Fig. 4: *Comparison of HBV DNA Load at baseline and after 24 months of treatment.*

in saloons, sharing personal items in joint families, organ transplantation, etc., are yet to be thoroughly explored at the community level.

In our study, the most dramatic change was noticed in HBV DNA level where a baseline mean of 343,52,823 (SD 1.02E+ 8) was reduced to a mean of 938 (SD 2051) with a t-value of 4.123 and a p-value of <0.001 after 24 weeks of treatment. This data re-affirms the excellent viral DNA suppression after initiating antivirals for treating HBV infection.

APRI score was improved in a statistically significant manner after 24 weeks of treatment, from a baseline mean of 1.06 (SD 0.59) to mean of 0.32 (SD 0.13), t-value 18.285, p-value <0.001. Similarly, FIB-4 index was improved from a baseline mean of 1.74 (SD 0.82) to 0.91 (SD 0.32), t-value 16.755, p-value <0.001 after 24 months.

FibroScan data showed that the mean baseline Median stiffness improved from 6.22 (SD 1.08) to mean of 4.87 (SD 0.76) with a p-value of <0.001. In astudy by Rong-Nan Chien *et al*, it was found that 85% patients had regression in fibrosis stage after successful treatment[12]. Our study corroborated the finding, with fibrosis regression been observed in 93% and no deterioration in the rest.

Genotyping and mutation studies were not done in this study as pan-genotypic regimen was used for treatment. Scant global data shows variability in the effect of standard of care treatment upon different genotypes.

Despite limitations, the data in this study further establishes the effect of antiviral agents in CHB infection while preventing hepatic decompensation, cirrhosis and HCC, fibrosis regression and viral seroconversion which lead to improvement in hepatic outcomes and overall prognosis.

Conclusion

We conclude that those who were infected with CHB mostly presented in 2nd to 4th decade and were diagnosed either incidentally or after a complication, mainly in the form of signs and symptoms suggesting portal hypertension. So, it is mandatory to perform HBsAg along with HBV DNA quantitative assay in all such patients. Patients who had achieved viral DNA load suppression, displayed a substantial FibroScan value decline, which correlated with the improvement in the non-invasive tests for fibrosis assessment like APRI and FIB-4. Whether the improvement of these non-invasive parameters in the form of APRI and FIB-4, alongside Median stiffness represent a real fibrosis regression or merely a resolution of chronic liver inflammation with subsequent improvements in FibroScan value and laboratory parameters have to be investigated by liver biopsy for better correlation between non-invasive and invasive methods. Again, the participants need to be followed-up for a longer duration to monitor long-term effects of antivirals while treating a CHB infection and its chronic complications. Moreover, the present study was a single centre study and the sample size was small to generalise the conclusions to the entire population.

Ethics statement and Consent

All procedures performed on participants were in accordance

with the ethical standards of the institutional and/or national research committee. Informed consent was obtained from the patients regarding the use of their clinical data. All the patient specific data was kept in strict confidence.

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