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A study on outcome of hepatic fibrosis in chronic hepatitis B patients on anti-viral therapy

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ABSTRACT

Background: Hepatitis B infection is a global public health problem. Chronic hepatitis B (CHB) infection leads to complications such as cirrhosis, liver failure, and hepatocellular carcinoma. Effective antiviral therapy significantly improves the stages of fibrosis in these patients. Hence, the liver stiffness measurement using transient elastography (Fibroscan) in CHB patients undergoing treatment is important to evaluate the effectiveness of the therapy and to predict the prognosis. **Aims and Objectives:** To see the outcome of Hepatic Fibrosis by non-invasive measurement in CHB patients after 6 months of oral anti-viral therapy. **Materials and Methods:** Seventy new CHB patients are included in a prospective hospital-based study and at the end of 6 months 53 patients were analysed. **Results:** Our study showed a significant statistical reduction in Liver Fibrosis as well as improvement of serological and biochemical parameters in CHB patients. **Conclusion:** There is liver fibrosis reversal in CHB patients after 6 months of anti-viral therapy and Fibroscan helps not only as a marker for initiation of treatment depending on the degree of fibrosis but also indicates the response or progression of the disease.

Key words: Chronic hepatitis B; Hepatitis B virus; Hepatic fibrosis; Fibroscan

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INTRODUCTION

Chronic Hepatitis B (CHB) remains a serious global public health concern affecting 400 million people.[1] Although the minority (only 15–40%) of infected individuals go on to develop chronic liver disease, liver failure, and hepatocellular carcinoma, this results in an estimated 0.5–1.2 million fatalities per year, ranking CHB as the tenth leading cause of death worldwide.[2,3] Chronic infection with hepatitis B virus (HBV) remains the predominant cause of chronic liver disease and liver-related morbidity worldwide.[4] Asia and the Western Pacific have the highest proportion of global CHB cases, with 75% of all CHB patients concentrated in these countries.[5] Chronic liver disease comprises a process of progressive destruction and regeneration of the liver parenchyma.[6] Liver fibrosis is known to result from chronic liver damage in conjunction with the excessive accumulation of extracellular matrix proteins, a characteristic of the majority of chronic liver disease types.[7] In the hepatic tissues of patients with CHB, the accumulation of extracellular matrix proteins distorts the hepatic architecture by forming a fibrous scar.[8] In CHB patients, there is accumulation of extracellular matrix proteins in the liver that distorts the hepatic architecture by forming fibrosis and the subsequent development of nodules of regenerating hepatocytes eventually leads to liver cirrhosis.[9] Therefore, it is crucial to achieve an accurate and timely diagnosis of liver fibrosis to prevent its development to liver cirrhosis. Moreover, long-

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term suppression of HBV with antiviral therapy significantly improves the stages of fibrosis in these patients. Hence, monitoring the stage of liver fibrosis in CHB patients undergoing anti-viral therapy is important to evaluate the effectiveness of the therapy and to predict the prognosis. Liver biopsy is considered to be the gold standard for the diagnosis of liver fibrosis. However, due to its invasiveness and high-cost the application of liver biopsy in the evaluation of liver fibrosis is limited. Liver stiffness measurement (LSM) using Transient Elastography (Fibroscan) is a non-invasive, rapid, quantitative, and low-cost transient method of assessing the degree of liver fibrosis. Briefly, vibrations of mild amplitude and low frequency are transmitted by the transducer, and induce an elastic shear wave that is propagated within the liver. Hence, in our study, we have tried to see the outcome of Hepatic Fibrosis by LSM in CHB patients after 6 months of oral anti-viral therapy in a Tertiary Teaching Centre of Eastern India.

Aims and objectives

To see the outcome of Hepatic Fibrosis by non-invasive measurement in CHB patients after 6 months of oral anti-viral therapy.

MATERIALS AND METHODS

This was a prospective hospital-based study. All newly diagnosed CHB patients requiring treatment were selected from General Medicine outdoor and indoor as well from liver clinic of Medical College and Hospital, Kolkata, West Bengal, a tertiary teaching institute of Eastern India. The study was approved by the ethics committee (IEC number-MC/KOL/IEC/NON-SPON/490/12-2016 dated December 10, 2016) of the hospital and informed consent was taken from all the subjects.70 CHB patients were selected in the study period from April 2017 to March 2018. Patients with decompensated chronic liver disease or with other co-infections such as HEPATITIS C, HIV, HEPATITIS A, E were excluded from the study. A detailed history was taken and a careful clinical examination was performed. The patients were initiated with oral anti-viral therapy (Tenofovir/Entecavir). Laboratory investigations such as liver function tests (LFT), prothrombin time (international normalized ratio), hepatitis B surface antigen, hepatitis B e antigen (HBeAg), HBV DNA levels and LSM by Transient Elastography (Fibroscan) were done in all patients at 0 and 6 months respectively. Other relevant investigations were done to rule out other systemic diseases. Out of the 70 patients enrolled, 2 died during follow-up and 15 patients were excluded from the study because 7 of them failed to turn up and 8 of them had poor drug adherence or compliance. Hence, at the end of the study, 53 patients were included and analyzed.

RESULTS

In the present study, we selected 70 CHB patients who fulfilled all our inclusion and exclusion criteria and after proper counselling and having written consent from each of them we put them on anti-viral therapy. Out of the 70 patients enrolled during the initial 6 months of study, 2 of them died during follow-up and 15 patients were excluded from the study because 7 of them failed to turn up and 8 of them had poor drug adherence or compliance. Hence, the final sample size came out to be 53 at the end of the study and our results and analysis were based on this sample size (n=53).

As shown in Table 1, the median age of the study population was 39.5 years ranging from 14 to 60 years. 32 (60.4%) were above 35 years of age and 21 (39.6%) were below 35 years of age. 35 (66%) were male and 18 (34%) were female. 21 (39.6%) patients were HBeAg reactive and 32 (60.4%) patients were HBeAg non-reactive. 30 (56.6%) were given entecavir (0.5 mg) and 23 (43.4%) were given tenofovir (300 mg) once daily and follow-up was done after 6 months. The baseline Child–Pugh Score was calculated based on the clinical and biochemical profiles of the patients and accordingly 67.9%, 26.4%, and 5.7% of patients belonged to CP Score A, B and C, respectively, before the initiation of therapy.

As shown in Table 2, The mean initial and follow-up Fibroscan Score or LSM by Transient Elastography in the total sample were found to be 14.42±11.69 kPa and 10.7±8.53 kPa respectively with a significant statistical reduction of 3.725 kPa (P<0.001). It was also observed that 46 (86.7%) patients showed a decrease in Fibroscan Score from the baseline, while 5 (9.4%) of them had an increase and 2 (3.7%) had the same score after 6 months of anti-viral therapy. Of the 53 patients, 56.6% who received Entecavir as an Anti-Viral Therapy showed a significant reduction in Fibroscan Scores with a mean reduction of 4.47 kPa (P<0.001) and 43.4% of patients who were on Tenofovir also had a significant reduction of 2.74 kPa (P=0.004) in Fibroscan Scores. When compared to the Two Cohorts by analysis of covariance (ANCOVA) Entecavir was not found to have a greater reduction potency in liver fibrosis compared to Tenofovir. Both HBeAg Reactive and Non- non-reactive groups also had significant reductions

Table 1: Baseline characteristics of patients

Characteristics	No. of patients (%)
Sex (M: F)	35:18
Age (mean year) (range)	39.5 (14–60)
HBeAg reactivity (%)	21 (39.6)
Tenofovir (%)	23 (43.4)
Entecavir (%)	30 (56.6)

HBeAg: Hepatitis B e antigen

Table 2: Comparison of fibroscan values in different subgroups

Variables	Fibroscan (baseline) Mean±SD	Fibroscan (6 month) Mean±SD	P-value
Total sample (n=53)	14.42±11.69	10.70±8.53	<0.001
Entecavir group (n=30)	15.46±12.95	10.99±9.42	<0.001
Tenofovir group (n=23)	13.07±9.91	10.32±7.39	0.004
HBeAg POS group (n=21)	19.84±15.54	14.73±11.19	0.001
HBeAg NEG group (n=32)	10.87±6.35	8.05±4.80	0.003
Child–Pugh group A (n=36)	11.24±7.58	8.98±5.77	0.001
Child–Pugh group B (n=14)	18.84±11.58	12.91±9.43	0.003
NO fibrosis group (n=11)	5.43±0.79	4.86±0.83	0.001
Significant fibrosis (n=21)	8.61±1.23	6.62±1.19	<0.001
Cirrhosis group (n=21)	22.87±8.33	16.39±7.56	<0.001

HBeAg: Hepatitis B e antigen

Table 3: Comparison of biochemical parameters

Variables	Baseline Mean±SD	6 month Mean±SD	P-value
Bilirubin (n=53)	3.40±6.32	0.87±0.45	0.005
SGPT (n=53)	119.38±163.58	41.58±23.31	0.001
SGOT (n=53)	103.08±128.31	40.34±17.40	0.001
Albumin (n=53)	3.90±1.48	4.05±0.38	0.008

SGPT: Serum glutamic-pyruvic transaminase, SGOT: Serum glutamic-oxaloacetic transaminase

in LSM with mean reductions of 5.11 kPa (P=0.001) and 2.81 kPa (P=0.003) after 6 months, respectively, but no group showed better significant reduction potency compared to the other one. The patients having Child–Pugh Scores A and B had significant reduction of Fibroscan Scores with mean reductions of 2.25 kPa (P=0.001) and 5.9 kPa (P=0.003), respectively. The 3 patients who were initially assessed as Child–Pugh Score C showed Fibroscan scores mean reduction but whether it was statistically significant or not could not be assessed because of the small sample size. However, all the 17 (19.7%) patients who were initially having Child–Pugh Scores B and C had shifted to Score A after 6 months of anti-viral treatment. The 3 Groups did not have any significant difference in Fibroscan reduction potency (as compared by ANCOVA).

All 53 patients were classified into 3 groups based on the initial LSM by Transient Elastography-

1. 11 (20.8%) patients having LSM <7V kPa (no significant fibrosis)
2. 21 (39.6%) patients having LSM >7 and <14 kPa (significant fibrosis)
3. 21 (39.6%) patients having LSM >14 kPa (cirrhosis).

Of the 21 patients who belonged to the Cirrhosis Group initially, 5 (23.8%) of them came to no fibrosis/significant fibrosis groups after 6 months. There were significant reductions in LSM in all the three groups with mean reductions of 0.72 kPa (P=0.03), 2.0 kPa (P<0.001) and 7.81 (P<0.001) in No fibrosis, significant fibrosis, and cirrhosis groups, respectively.

Apart from Fibroscan Score, all the 53 patients had monitoring of LFT and HBV DNA levels at 0, 6 months as surrogate markers of treatment response. The total bilirubin mean value was significantly reduced by 2.53 mg/dL (P=0.005). Both the liver enzymes serum glutamic-pyruvic transaminase (SGPT) and serum glutamic-oxaloacetic transaminase (SGOT) also had significant mean reductions of 77.79 IU/mL (P=001) and 62.7 IU/mL (P=0.001). The Albumin value on the other hand was significantly increased from 3.9 mg/dL to 4.05 mg/dL (P=0.008) (Table 3).

DISCUSSION

In the present study, among the large pool of patients, we came across every day in our Medical College and Hospital we selected 70 CHB patients who fulfilled all our inclusion and exclusion criteria and after proper counseling and have written consent from each of them, we put them on anti-viral therapy (Tenofovir 300 mg/Entecavir 0.5 mg once daily) with subsequent follow-up done at liver clinic. However, owing to several reasons as cited before, only 53 patients could be followed up till the end of the study.

Among these 53 patients, 35 (66%) were males and 18 (34%) were females. The median age of the study population was 39.5 years ranging from 14 to 60 years. In a study performed by Kim et al., in the year 2014 among 83 Chinese CHB Patients, there were 61 (73.5%) men and 22 (26.5%) women, with a median age of 51.5±9.1 years but the mean interval between two LSMs was longer (411.5±149.5 days) compared to our study where follow up was done after 180 days.[10]

In our study, 39.6% of patients were HBeAg Reactive and 60.4% of patients were HBeAg Non-Reactive. The baseline Child–Pugh Score was calculated and accordingly 67.9%, 26.4%, and 5.7% of patients belonged to CP Score A, B, and C, respectively, before the initiation of therapy. Thirty (56.6%) of them were given Entecavir (0.5 mg) and 23 (43.4%) were given Tenofovir (300 mg) once daily and

follow-up was done after 6 months. In the same study, performed by Kim et al., the HBeAg rate was 53% and the anti-viral therapy that was advocated were entecavir 0.5 mg in 28 (33.7%), lamivudine in 22 (26.5%), clevudine in 14 (16.9%), adefovir in 4 (4.8%), lamivudine plus adefovir in 11 (13.3%), and entecavir 1.0 mg in 4 (4.8%) patients.[10]

The mean initial and follow-up Fibroscan Score or LSM by Transient Elastography were found to be 14.42 kPa and 10.7 kPa respectively with a significant statistical reduction of 3.725 kPa (P<0.001). In a study conducted by Osakabe et al., in 2011, among CHB patients treated with either entecavir or lamivudine for 3 years, it was observed that LSM values decreased significantly from baseline to 1, 2, and 3 years after treatment (medians 12.9 kPa, 7.5 kPa, 6.5 kPa, and 4.7 kPa, respectively; all P<0.05).[11] In the study performed by Kim et al., it was found that initial and follow-up LSM was 16.15±12.41 kPa and 11.26±7.36 kPa, respectively (P<0.001). The degree of regression of liver stiffness was −2.03±0.36% per month.[10]

There were significant statistical reductions of LSM in both young and old patients having a mean reduction of 3.9 kPa (P=0.007) and 3.59 kPa (P<0.001), respectively. The Fibroscan Scores were also significantly reduced in both males and females with a mean reduction of 4.12 kPa (P<0.001) and 2.956 kPa (P=0.009) respectively. The patients having Child–Pugh Scores A and B had significant reduction of Fibroscan Scores with mean reductions of 2.25 kPa (P=0.001) and 5.9 kPa (P=0.003), respectively. The 3 patients who were initially assessed as Child–Pugh Score C showed a mean reduction in Fibroscan Scores, but whether it was statistically significant or not could be assessed because of small sample size. However, all the 17 (19.7%) patients who were initially having Child–Pugh Scores B and C had shifted to Score A after 6 months of anti-viral treatment.

Of the 21 patients who belonged to the Cirrhosis Group initially, 5 (23.8%) of them came to No Fibrosis/Significant Fibrosis Groups after 6 months. There were significant reductions in LSM in all the three groups with mean reductions of 0.72 kPa (P=0.03), 2.0 kPa (P<0.001) and 7.81 (P<0.001) in no fibrosis, significant fibrosis, and cirrhosis groups respectively. In a retrospective study conducted by Kuo et al., in 2014, 233 patients were enrolled including 132 without cirrhosis (group 1) and 101 with cirrhosis (group 2) it was found that in non-cirrhotic patients the baseline and follow-up LSMs were 6.5 kPa and 5.4 kPa respectively. As for the patients in group 2 that is in cirrhotic patients, the median initial and follow-up LSMs were 12.5 kPa and 10.1 kPa, respectively.[12]

Of the 53 patients, 56.6% who received Entecavir as an Anti-Viral Therapy showed a significant reduction in Fibroscan Scores with a mean reduction of 4.47 kPa (P<0.001) and 43.4% of patients who were on Tenofovir also had a significant reduction of 2.74 kPa (P=0.004) in Fibroscan Scores. When compared to the Two Cohorts by ANCOVA Entecavir was not found to have a greater reduction potency in liver fibrosis compared to Tenofovir. In a study conducted by Güzelbulut et al., among 44 CHB patients, 24 received entecavir and 20 received tenofovir. The mean histological activity index score improved by 3.83±3.51 points in the entecavir group and 2.20±1.91 points in the tenofovir group (P=0.07), and the mean fibrosis scores improved by 0.38±1.61 points in the entecavir group and 0.70±1.17 points in the tenofovir group after 48 weeks (P=0.44), respectively. Both Entecavir and tenofovir were found to be similarly effective in nucleos(t)ide-naive CHB patients with high viral load and/or high fibrosis scores after 48 weeks of therapy.[13] Both HBeAg Reactive and Non- non-reactive groups also had significant reductions in LSM with mean reductions of 5.11 kPa (P=0.001) and 2.81 kPa (P=0.003) after 6 months respectively but no group showed better significant reduction potency compared to the other one.

Apart from Fibroscan Score, all the 53 patients had monitoring of LFT and HBV DNA levels at 0, 6 months as surrogate markers of treatment response. The total bilirubin mean value was significantly reduced by 2.53 mg/dL (P=0.005). Both the liver enzymes SGPT and SGOT also had significant mean reductions of 77.79 IU/mL (P=001) and 62.7 IU/mL (P=0.001). The Albumin value on the other hand was significantly increased from 3.9 mg/dL to 4.05 mg/dL (P=0.008). Among the 46 (86.7%) patients where there was reduction in Fibroscan Score, all the other parameters like HBV DNA, SGPT and SGOT got significantly reduced (P<0.001). Although in 5 (9.4%) patients there was increase in liver fibrosis, the biochemical and serological parameters got significantly reduced (P<0.05).

In the study conducted by Kuo et al., corroborative with our present study there were improvements of serological and biochemical parameters apart from significant LSM reductions. The median initial ALT and follow-up ALT was 37.5 IU/L and 26 IU/L for non-cirrhotic as well as 37 IU/L and 33 IU/L for cirrhotic patients respectively with a significant decrease of ALT in both groups (P<0.001). HBV DNA level also had a significant decrease in both groups from (3.64±2.6 IU/L to 1.26±0.6 IU/L (P<0.001) in non-cirrhotic patients and 3.53±2.5 IU/L to 1.1±0.2 IU/L (P<0.001) in the cirrhotic group respectively.[12] In a prospective observational study conducted by Cho et al., 36 treatment naïve CHB patients started on tenofovir disproxil fumarate demonstrated a significant decrease in LSM values from 13.8 kPa at baseline to 8.7 kPa, 6.5 kPa, and 6.4 kPa at weeks 48, 96, and 144 of therapy, respectively (all

P<0.001).[14] In a retrospective analysis conducted by Gai and Wu 46 compensated CHB patients (compensated group) and 51 decompensated CHB patients (decompensated group) were treated with entecavir. Both groups showed a decrease in liver stiffness decreased with time. Liver stiffness was observed to be significantly lower in the compensated group compared with the decompensated group at weeks 24, 48, and 96 (P<0.05).[15] In a systematic review and meta-analysis of 24 studies in adults with hepatitis B who underwent transient elastography before and at least 6 months after starting nucleot(s)ide analogs therapy, Facciorusso et al., noted that liver stiffness decreased by 2.21 kPa (95% CI, −1.36–−3.05), 2.56 kPa (−2.23–−2.89), 3.73 kPa (−2.98–−4.49), 4.15 kPa (−2.75–−5.54), and 5.19 kPa (−3.34–−7.03) at 6 months, 1 year, 2 years, 3 years, and 5 years from the initiation of therapy, respectively (P<0.001). A high baseline alanine aminotransferase level, viral load and liver stiffness were associated with a greater degree of decrease in liver stiffness.[16] Thus, as per previous studies, our present study also showed a significant reduction in Liver Fibrosis as well as an improvement of serological and biochemical parameters but in a shorter follow-up time frame of 6 months compared to these studies.

Limitations of the study

Our study was carried out in a small population of patients and within a very short period of time(1 year). We must say that further long term , multi-centric, multi-arm studies involving large patient group are necessary in this regard.

CONCLUSION

Thus, in the final conclusion, it can be stated that there is liver fibrosis reversal in CHB patients after 6 months of anti-viral therapy and fibroscan helps not only as a marker for the initiation of treatment depending on the degree of fibrosis but also indicates the response or progression of the disease.

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AN- Definition of intellectual content, literature survey, prepared first draft of manuscript; implementation of study protocol, data collection, data analysis, manuscript preparation and submission of article; **SG**- Design of study, statistical analysis and interpretation; **SS**- Concept, design, clinical protocol, manuscript preparation, editing, and manuscript revision; **SSM**- Review Manuscript; **EH**- Review manuscript**; SKM**- Literature survey and preparation of figures, coordination and manuscript revision.

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