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Status of liver stiffness following directly acting antiviral treatment in patients with chronic hepatitis C: A Nepalese study

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ABSTRACT

Background & Objectives: Chronic hepatitis C is one of the leading causes of chronic liver disease in our country. With the introduction of directly acting antivirals, many patients are benefitted these days. Transient elastography is one of the newer technologies for measuring liver stiffness and quantifying liver fibrosis and has excellent accuracy for the diagnosis of fibrosis in patients with chronic hepatitis C. Our study analyzes changes of liver stiffness and its associated factors in patients with chronic hepatitis C treated with directly acting antivirals (DAAs). **Materials & Methods:** One hundred and seven patients with chronic hepatitis C, who were treated with DAAs (Sofosbuvir 400 mg and velpatasvir 100mg) and have significant fibrosis (>7.0 kPa) at baseline were included. Liver stiffness was measured at the time of enrollment, and after completion of DAAs with fibroscan and changes of stiffness and its associated factors were analyzed. **Results:** The study showed significant decrease in liver stiffness at the end of treatment, which continued after treatment only in patients who achieved a sustained virological response. **Conclusion:** Liver stiffness decreased following 12 weeks of successful DAAs therapy in patients with chronic hepatitis C at the end of treatment who achieved sustained virological response.

Key words: Chonic hepatitis; Directly acting antivirals; fibrosis; liver stiffness

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INTRODUCTION

Chronic hepatitis C is one of the leading causes of chronic liver disease in our country. Nowadays, HCV is becoming the first cause of primary liver cancer and is the main indication for liver transplantation in industrialized countries. Chronic hepatitis C is responsible for substantial morbidity and mortality related to liver cirrhosis and its complications, including hepatocellular carcinoma.[1, 2, 3] With the availability of DAAs in the market, the current standard treatment of chronic hepatitis C is the combination of different directly acting antivirals.[4] The liver fibrosis stage is the principal predictor of liver disease progression and it determines the treatment indications. Liver biopsy examination has traditionally been considered the reference method for staging liver fibrosis but with the high accuracy rate of non-invasive procedure like transient elastography, current guidelines also suggest the use of such approach in evaluating chronic hepatitis C patients and monitoring and evaluation of disease status during and after treatment. Transient elastography by means of the Fibroscan (Echosens, Paris, France) measures liver stiffness. It can be performed at the bedside with immediate results and has been reported to be rapid, user-friendly and reproducible. Liver stiffness has been shown to correlate with the hepatic fibrosis stage and has excellent accuracy for the diagnosis of cirrhosis in patients with chronic hepatitis C.[5, 6] There are few studies in the past analyzing the kinetics of liver stiffness in patients with chronic hepatitis C receiving antiviral therapy with pegylated interferon and ribavirin,[7] but no such type

of study was done in our country. The goal of this study was to retrospectively analyze the changes of liver stiffness and its associated factors in patients with chronic hepatitis C treated with DAAs before treatment and after treatment with DAAs.

MATERIALS AND METHODS

One hundred and seven patients diagnosed with chronic hepatitis C, i.e. patients with detectable serum anti-HCV antibodies and HCV RNA and elevated serum alanine aminotransferase (ALT) levels, who came to outpatient department of center for liver disease, Kathmandu, Nepal, were included in this study. All of them were treatment-naïve and the main inclusion criteria was significant fibrosis, defined as liver stiffness >7.0 kilopascals (kPa) measured by Fibroscan. The exclusion criteria were: coinfection with hepatitis B virus or human immunodeficiency virus (HIV), a daily alcohol intake >30 g, decompensated liver disease or hepatocellular carcinoma, liver transplantation, and a failed or unreliable liver stiffness. Patients received standard-of-care therapy with oral directly acting antivirals (Sofosbuvir 400 mg and vepatasvir 100 mg) once a day for 12 weeks in patients infected with HCV irrespective of genotypes. ALT levels, HCV RNA levels and liver stiffness, and APRI (AST to Platelets Ratio Index) score were evaluated at baseline and after 12 weeks of therapy in all patients. The sustained virological response (SVR) was defined as an undetectable HCV RNA 12 weeks after receiving DAAs. HCV RNA levels were measured centrally by means of the real-time PCR platform (Abbott Molecular, Des Plaines, Illinois), with standard protocol. The lower limit of detection was 15 IU/mL.

Liver stiffness measurements were performed with the FibroScan device by ECHOSENS, France. Ten validated measurements were performed for each patient. The success rate was calculated as the number of validated measurements divided by the total number of measurements. The results were expressed in kilopascals. The median value was considered representative of the elastic modulus of the liver. Only procedures with at least ten successful acquisitions, a success rate of at least 60% and an interquartile range (IQR) of less than 30% of the median value were considered reliable.

Data were analyzed using SPSS version 20.Continuous variables were expressed as mean. Categorical variables are depicted as absolute numbers and percentages. Data were analyzed using two tailed pair t tests. A p-value below 0.05 was considered statistically significant.

RESULTS

The mean age of patients was 34.34 ± 9.5 years with a minimum of 20 years and maximum of 70 years. The baseline characteristics of the patients are shown in table 1.The mean pretreatment viral load was 1.1 X 106 IU/ml and post treatment viral load after 12 weeks of therapy was undetectable that is less than 15IU/ml . The mean pretreatment ALT was105.68 ± 66.43 U/Land post treatment ALT was 59.46 ± 24.52U/L. The mean pretreatment AST was 88.19 ± 43.25U/L and post treatment AST was 51.70 ± 13.96 U/L (table 2). There was significant decrease in APRI score and liver stiffness following 12 weeks of therapy (p 0.000) (table 2).

DISCUSSION

Successful therapy with directly acting antivirals with or without ribavirin has been shown to be associated with significant histological improvements in previous studies.[7,8] Follow-up liver biopsy is not a part of routine management of patients with chronic HCV infection receiving antiviral therapy due to its invasive nature and less patient's compatibility. So, non-invasive methods like transient elastography appear to be better option for monitoring of therapeutic response in these patients during and after therapy.[9,10] Given its simplicity, high acceptability by patients and intrinsic performance, transient elastography is already become an appropriate tool for the longitudinal follow-up of fibrosis changes in treated HCV-infected patients,[11] as shown in the present study.

Table 1. Baseline Patient Characteristics

Parameters		n (%)
Male		93 (86.9)
Female		14 (13.1)
Normal USG		96 (89.7)
Chronic liver disease		11 (10.3)
Genotype	1a	44 (41.1)
	1b	1 (0.9)
	1c	2 (1.9)
	2a	2 (1.9)
	2b	1 (0.9)
	3a	50 (46.7)
	3b	7 (6.5)
Total		**107**

Table 2: Comparison of APRI and liver stiffness pre and post treatment

Parameters	Mean ± Std. deviation		
	Pre treatment	Post treatment	
APPRI	1.47 ± 0.883	0.84 ± 0.438	P<0.000
Liver stiffness(kpa)	11.78 ± 5.199	7.64 ± 2.731	

In our study, we analyzed the dynamics of liver stiffness in patients with significant fibrosis at baseline treated with DAAs. Liver stiffness and HCV RNA kinetics were assessed before and after therapy and compared. We observed that liver stiffness significantly decreased in patients with chronic HCV infection after successful treatment with 12 weeks of DAAs and those who achieve SVR. In addition, our study also showed there is a significant decrease in APRI score after 12 weeks of DAA therapy which also correlates with the decrease in liver stiffness of these patients.

Our study suggests that the cure of chronic hepatitis C virus infection is associated with a significant reduction of liver stiffness, as measured by transient elastography. This result may appear surprising as transient elastography is claimed to assess essentially the fibrotic component of liver lesions, while treatment has been mostly associated with reduction of the inflammatory reaction in the liver. Two hypotheses can explain this result: (i) liver stiffness is also influenced by the local inflammatory reaction; (ii) fibrosis significantly regresses on treatment and thereafter in patients who achieve an SVR. The first hypothesis may appear unlikely as no relationship was observed between liver stiffness changes and ALT kinetics; however, ALT elevations do not always accurately reflect liver inflammation. On the other hand, SVR was the sole predictor of long-term liver stiffness improvement; nevertheless, SVR is also associated with an improvement of liver inflammation. Therefore, this hypothesis cannot be definitively ruled out. Indeed, others have reported an overestimation of liver stiffness in patients with liver inflammation reflected by high ALT level.[12, 13] In addition, a significant decrease of liver stiffness was observed during therapy, followed by an increase after treatment withdrawal, in the patients from previous study who did not clear HCV infection. Histological data might have helped to resolve this question. However, liver biopsy is no longer routinely performed during or after antiviral treatment for poor patient's compliance.[14] Therefore, this question will remain unanswered.

Our hypothesis concerning liver stiffness changes in patients who achieved an SVR witnessing fibrosis regression is in keeping with the reported improvement of histological fibrosis in a similar population who underwent paired liver biopsies.[15] It is also in keeping with the lower incidence of clinical outcomes, including liver failure, variceal bleeding or hepatocellular carcinoma, in patients with cirrhosis who achieved an SVR.[16] However, patients with cirrhosis who achieved SVR experienced a significant improvement of their liver stiffness after 12 weeks of therapy in our study, their median liver stiffness values remained significantly higher than in patients without cirrhosis who achieved an SVR. In this context, the fact that the risk of developing HCC remains substantial in cirrhotic patients who achieved an SVR is not surprising.

The results of this study show that transient elastography can be used to monitor liver stiffness changes during and after antiviral therapy in patients with chronic hepatitis C. On average, in patients with advanced fibrosis at the start of therapy, liver stiffness is significantly reduced after successful treatment with DAAs. The significant reduction of liver stiffness continues off treatment only in patients who achieve SVR. This probably denotes fibrosis regression, although it cannot be ruled out that improvements in the inflammatory reaction in these patients may also influence liver stiffness changes. These findings suggest that assessing liver stiffness by means of transient elastography at baseline and 12 weeks after treatment in patients who achieve an SVR is useful to assess the global response to antiviral therapy, establish a prognosis and serve as a basis for subsequent follow-up in patients with advanced fibrosis, especially those with cirrhosis.

CONCLUSION

Liver stiffness decreased following 12 weeks of successful DAAs therapy in patients with chronic hepatitis C at the end of treatment who achieved

sustained virological response.

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