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Shear Wave Velocity Improves in Hepatitis C Patients Treated with Direct-Acting Antiviral Agents

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Abstract

Purpose: The purpose of this study was to observe the changes over time in the Velocity of the Shear wave (Vs) in Hepatitis C patients during Direct-Acting Antiviral agent (DAA) treatment.

Methods: Shear Wave Elastography (SWE) was performed at baseline, at the End of Treatment (EOT), and 12 weeks (follow-up 12) and 24 weeks (follow-up 24) after EOT in Hepatitis C patients. Alanine Aminotransferase (ALT), Alpha-Feto Protein (AFP), and Mac-2 Binding Protein Glycosylation isomer (M2BPGi) levels were measured at the same times.

Results: Data from 92 patients were analyzed. Mean Vs measured by SWE was high (1.57 m/s ± 0.29 m/s), but it decreased significantly to 1.46 m/s ± 0.27 m/s during the 12-week DAA treatment period. Vs at follow-up 12 further decreased significantly to 1.42 m/s ± 0.25 m/s, but later plateaued. ALT and AFP also decreased significantly from baseline to follow-up 12, followed by a plateau. Mean M2BPGi decreased significantly from 2.93 ± 2.62 Cut-Off Index (C.O.I.) at baseline to 1.58 C.O.I. ± 1.30 C.O.I. at EOT (p=0.00000). Mean M2BPGi decreased significantly until follow-up 12 (p=0.00045) and then tended to further decrease at follow-up 24 (p=0.09807).

Conclusion: Vs measured using SWE in Hepatitis C patients improved with 12 weeks of DAA therapy. This improvement continued until follow-up 12 and then plateaued.

Keywords: Direct-acting antiviral agent; Hepatitis C; Mac-2 binding protein glycosylation isomer; Shear wave elastography; Velocity of the shear wave

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Introduction

Significant advances have been made in the treatment of Hepatitis C with the advent of Direct-Acting Antiviral agents (DAAs). DAA therapy has milder side effects than Interferon (IFN) therapy, and there is a high rate of Sustained Virological Response (SVR) at 12 weeks [1-5]. In Hepatitis C patients, however, SVR is not the only therapeutic target; hepatocarcinogenesis must also be held in check. Liver fibrosis is a strong contributor to the development of Hepato Cellular Carcinoma (HCC), and it is reported to improve in patients who achieve long-term SVR with IFN therapy [6,7].

In recent years, methods that measure liver stiffness non-invasively with ultrasound, including Acoustic Radiation Force Impulse Imaging (ARFI) [8], Transient Elastography (TE) [9], and Strain Elastography (SE) [10], have been reported to be useful in evaluating hepatic fibrosis. Two-Dimensional Shear Wave Elastography (2D-SWE) is a new technology that gauges liver stiffness by measuring the propagation velocity of shear waves generated in liver tissue. Vs measurements with 2D-SWE are reported to be useful in diagnosing fibrosis in Hepatitis C [11]. There is a close linkage between the elasticity modulus measured by 2D-SWE and the presence of HCC in patients with a sustained virological response to interferon for chronic Hepatitis C [12]. However, in studies using TE, the Velocity of the Shear wave (Vs) was affected not only by liver fibrosis, but also by necroinflammatory activity [13,14].

We previously reported that, in Hepatitis C patients, Vs on 2D-SWEwas higher in the naïve group than in the SVR group, presumably due to Hepatitis activity [15]. The purpose of this study was to observe the changes over time in Vs in Hepatitis C patients during DAA treatment.

Patients and Methods

This prospective study was approved by the Ethics Committee of Dokkyo Medical University, Saitama Medical Center (No. 1575), and written; informed consent was obtained from all

Table 1: Patient characteristics (n=92).

Age (yr)	64.6 ± 12.2
Sex (male/female)	39/53
Serotype (1/2)	53/39
IFN (Yes/No)	32/60
HCV RNA (Log IU/ml)	5.8 ± 0.9
ALT (IU/L)	60.7 ± 44.1
Total bilirubin (mg/dL)	0.86 ± 0.31
Serum albmin (g/dL)	4.23 ± 0.35
WBC (× 10^3/mm^3)	5.09 ± 1.68
Hb (g/dL)	14.0 ± 1.4
Platelet (× 10^4/mm^3)	15.7 ± 5.3
Prothrombin activity (%)	101.0 ± 16.8
AFP (g/dL)	10.2 ± 20.2
Fib4 index	3.56 ± 2.70
M2BPGi (C.O.I.)	2.93 ± 2.64
Vs (m/s)	1.58 ± 0.29

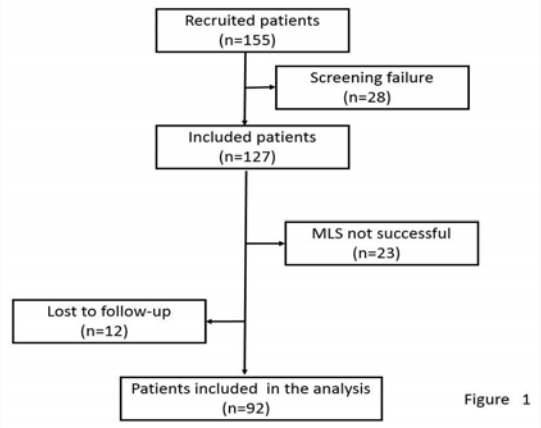

Figure 1: Flowchart of the study.
A total of 155 consecutive Hepatitis C patients were recruited for the study. Patients with a history of HCC (n=6), fatty liver (n=15), co-existing autoimmune hepatitis (n=1), history of cardiac failure (n=1), and those who consumed large amounts of alcohol (n=5) were later excluded as screening failures. Twenty-three patients in whom Measurement of Liver Stiffness (MLS) was unsuccessful and 12 patients lost to follow-up were also excluded. Therefore, data from 92 patients were used for the analysis.

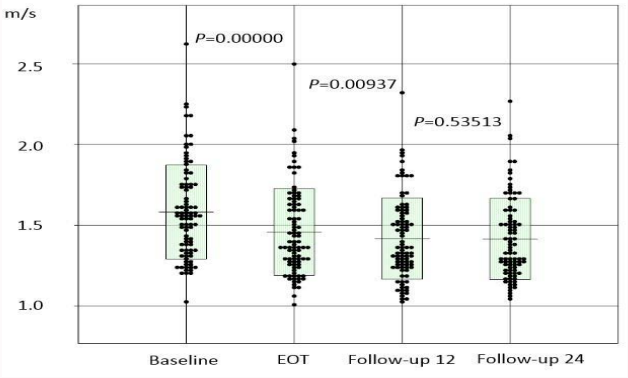

Figure 2: Changes in Vs from baseline to follow-up 24.
Mean Vs is 1.57 m/s ± 0.29 m/s at baseline, 1.46 m/s ± 0.27 m/s at EOT, 1.42 m/s ± 0.25 m/s at follow-up 12, and 1.41 m/s ± 0.23 m/s at follow-up 24. The differences between baseline and EOT and between EOT and follow-up 12 are significant (p=0.00000 and p=0.00937, respectively). However, the difference between follow-up 12 and follow-up 24 is not significant (p=0.53513).

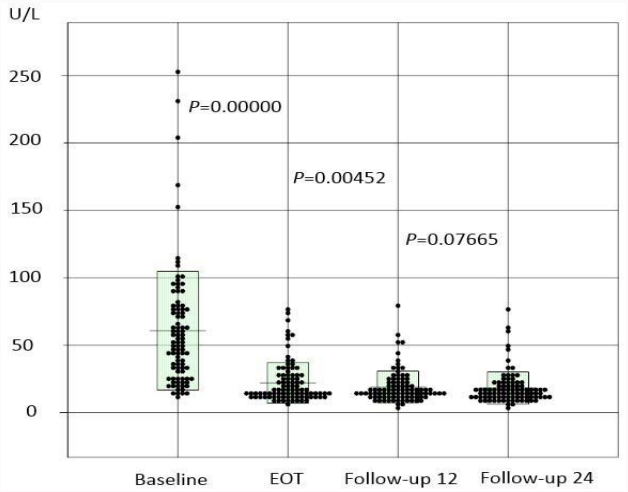

Figure 3: Changes in ALT from baseline to follow-up 24.
Mean ALT is 60.7 IU/L ± 44.1 IU/L at baseline, 22.1 IU/L ± 15.0 IU/L at EOT, 19.0 IU/L ± 11.8 IU/L at follow-up 12, and 18.3 IU/L ± 12.0 IU/L at follow-up 24. The differences between baseline and EOT and between EOT and follow-up 12 are significant (p=0.00000 and p=0.00452, respectively). However, the difference between follow-up 12 and follow-up 24 is not significant (p=0.07665).

participants. This study conformed to the ethical guidelines of the 2008 Declaration of Helsinki. The subjects were 155 consecutive patients diagnosed with Hepatitis C in the Department of Gastroenterology, Dokkyo Medical University, Koshigaya Hospital, to whom treatment with DAAs was given between July 2015 and May 2016.

2D-SWE was performed before starting treatment (baseline), at the End of Treatment (EOT), and 12 weeks (follow-up 12) and 24 weeks (follow-up 24) after EOT. Alanine Aminotransferase (ALT), Alpha-Feto Protein (AFP), and Mac-2 Binding Protein Glycosylation isomer (M2BPGi) levels were measured on the same days as 2D-SWE. With the cooperation of some patients, similar measurements were also performed at 4 weeks and 8 weeks after starting treatment.

Patients with decompensated liver cirrhosis, hepatocellular carcinoma, autoimmune disease, collagen disease, or chronic heart disease were excluded. Patients with a history of drinking ≥ 20 g alcohol per day and those diagnosed with obvious fatty liver on abdominal ultrasound were also excluded.

Measurement of the velocity of the shear wave

Measurement of Vs by 2D-SWE was performed using a LOGIQ E9 (GE Healthcare, Milwaukee, WI). The right lobe of the liver was visualized through an intercostal space while the patient was lying in a supine position with the right arm in maximum abduction. Measurements were taken while subjects held their breath during spontaneous breathing. The visual depth of the system was fixed at 8 cm, and the Region of Interest (ROI) was 1 cm to 2 cm below the surface of the liver. The system was adjusted so that samples volume depth was 4 cm or less. The apparatus automatically calculated the Vs and the results are expressed in m/s. The result was considered reliable only when 10 successful shots and a measurement success rate >80% were obtained.

Clinical parameters

Clinical parameters, which were obtained on the same day that 2D-SWE was performed, were compared. Clinical parameters other than Vs were the following: Alanine Aminotransferase (ALT), AFP, and Mac-2 Binding Protein Glycosylation-isomer (M2BPGi).

Evaluation of patients for heap to cellular carcinoma

B-mode ultrasound was performed on the same day as 2D-SWE to assess patients for HCC. B-mode ultrasound was also performed once at 6 months after follow-up 24. If a tumor was detected on B-mode ultrasound, contrast Computed Tomography (CT) or Gadolinium Ethoxybenzyl Diethylenetriamine Pentaacetic Acid (Gd-EOB-DTPA) Magnetic Resonance Imaging (MRI) was performed for confirmatory diagnosis. Serial changes in Vs, ALT, AFP, and M2BPGi were evaluated in individual patients who developed HCC.

Statistical analysis

Continuous data for liver stiffness and other clinical parameters are expressed as means ± Standard Deviation (SD). A paired Wilcoxon test was used to test for differences in each parameter before and after the start of treatment. Friedman's test was used to test multiple comparisons of each parameter. Values of $p<0.05$ were regarded as significant.

Results

A total of 155 consecutive Hepatitis C patients were recruited for the study. Twenty-eight of these patients, including six patients with a history of HCC, 15 patients diagnosed with fatty liver by ultrasound, one patient with co-existing autoimmune Hepatitis, one patient with a history of cardiac failure, and five patients with a history of drinking ≥ 20 g/day of alcohol, were excluded. Another 12 patients in whom liver stiffness could not be measured because of obesity or hepatic atrophy and 11 patients with large measurement errors were also excluded from the evaluation. In addition, another 12 patients, including seven patients who discontinued their hospital visits after DAA therapy and five patients without periodic 2D-SWE measurements, were withdrawn from the study. Therefore, data from 92 patients were finally used for the analysis (Figure 1).

The DAAs used for treatment in these 92 patients were Sofosbuvir (SOF)/Ledipasvir (LDV) in 40 patients, ombitasvir/paritaprevir/ritonavir in 14 patients, and SOF/ribavirin in 38 patients. Table 1 shows the characteristics of the 92 patients (39 men, 53 women; mean age 64.6 ± 12.2 years). Thirty-two patients (35.6%) had previously received IFN therapy. Their mean ALT was 60.7 IU/L ± 44.1 IU/L, including a large number of Hepatitis patients with relatively highly active disease. Other biochemical values, AFP, M2BPGi, and Vs, were consistent with Chronic Hepatitis. DAA therapy was continued for 12 weeks. All 92 patients achieved SVR at 24 weeks after the EOT.

Changes in parameters from baseline to follow-up 24

Figure 2 shows the changes in Vs. Mean Vs decreased significantly during the 12-week treatment period from 1.57 m/s ± 0.29 m/s at baseline to 1.46 m/s ± 0.27 m/s at EOT (p=0.00000). Mean Vs at follow-up 12 was 1.42 m/s ± 0.25 m/s, a significant decrease from the Vs at EOT (p=0.00937). The mean Vs at follow-up 24 was 1.41 m/s ± 0.23 m/s, with no significant difference from follow-up 12 (p=0.53513).

Mean ALT decreased significantly during the 12-week treatment period from 60.7 IU/L ± 44.1 IU/L at baseline to 22.1 IU/L ± 15.0 IU/L at EOT (p=0.00000). Mean ALT, like Vs, further decreased significantly until follow-up 12 (p=0.00452), but there was no significant difference between follow-up 12 and follow-up 24 (p=0.07665) (Figure 3).

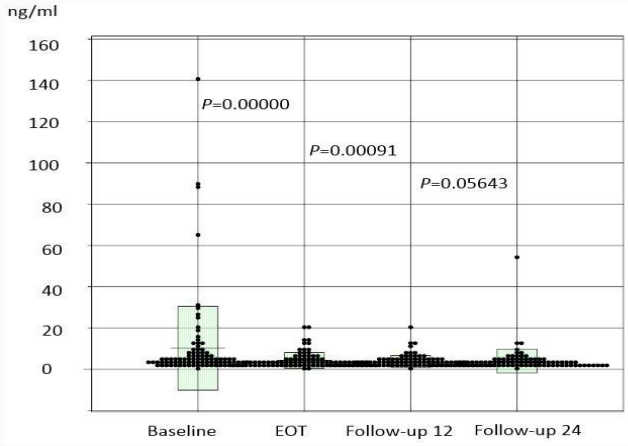

Figure 4: Changes in AFP from baseline to follow-up 24.
Mean AFP is 10.2 ng/ml ± 20.2 ng/ml at baseline, 4.33 ng/ml ± 3.77 ng/ml at EOT, 3.76 ng/ml ± 2.89 ng/ml at follow-up 12, and 3.98 ng/ml ± 5.77 ng/ml at follow-up 24. Only one patient has a high AFP (54.6 ng/ml) at follow-up 24. The differences between baseline and EOT and between EOT and follow-up 12 are significant (p=0.00000 and p=0.00091, respectively). However, the difference between follow-up 12 and follow-up 24 is not significant (p=0.05643).

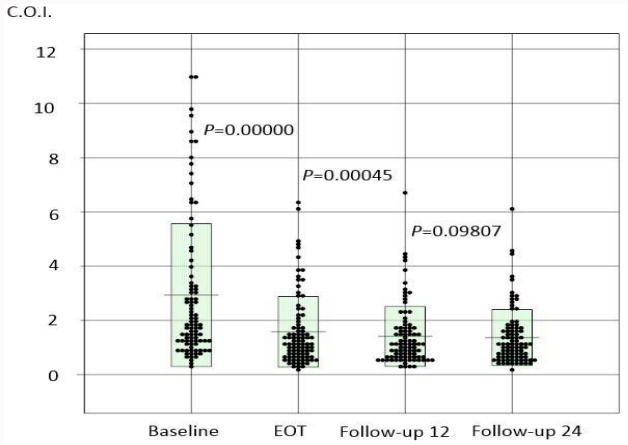

Figure 5: Changes in M2BPGi from baseline to follow-up 24.
Mean M2BPGi is 2.93 C.O.I. ± 2.62 C.O.I. at baseline, 1.58 C.O.I. ± 1.30 C.O.I. C.O.I. at EOT, 1.41 C.O.I. ± 1.11 C.O.I. at follow-up 12, and 1.37 C.O.I. ± 1.03 C.O.I. at follow-up 24. The differences between baseline and EOT and between EOT and follow-up 12 are significant (p=0.00000 and p=0.00045, respectively). However, the difference between follow-up 12 and follow-up 24 is not significant (p=0.09807).

Mean AFP was 10.2 ng/ml ± 20.2 ng/ml at baseline, 4.33 ng/ml ± 3.77 ng/ml at EOT and 3.76 ng/ml ± 2.89 ng/ml at follow-up 12. The decreases in AFP were significant from baseline until follow-up 12 (p=0.00000, p=0.00091). Mean AFP at follow-up 24 was 3.98 ng/ml ± 5.77 ng/ml, with no significant difference from follow-up 12 (p=0.05643). Only one patient had a high AFP (54.6 ng/ml) at follow-up 24 (Figure 4).

Mean M2BPGi decreased significantly from 2.93 ± 2.62 Cut-Off Index (C.O.I.) at baseline to 1.58 C.O.I. ± 1.30 C.O.I. at EOT (p=0.00000). Mean M2BPGi, like Vs, ALT, and AFP, decreased significantly until follow-up 12 (p=0.00045). M2BPGi tended to

further decrease at follow-up 24, but the difference was not significant (p=0.09807) (Figure 5).

On multiple comparisons of Vs, ALT, AFP, and M2BPGi using Friedman's test, significant differences were found in each parameter (p=0.00000).

Presentation of patients who developed hepatocellular carcinoma

Among all 92 patients further monitored for at least 1 year after follow-up 24 (mean observation period: 1.8 years), HCC occurred in only one patient.

The baseline Vs of this patient was 2.06 m/s, and the EOT Vs was 2.04 m/s, without significant change. The Vs at follow-up 12 decreased to 1.82 m/s, but it remained about the same (1.80 m/s) at follow-up 24. Surgical resection of the HCC was performed, and histopathology of a surgical specimen showed marked fibrosis with only very mild inflammatory cell infiltration.

Discussion

Vs as measured by 2D-SWE are about 1.2 m/s in normal livers [15]. Mean Vs was high, at 1.57 m/s ± 0.29 m/s, in the present Hepatitis C patients, but it did decrease significantly to 1.46 m/s ± 0.27 m/s during a short 12-week period of DAA therapy. Vs at follow-up 12further decreased significantly to 1.42 m/s ± 0.25 m/s, but Vs later plateaued. ALT and AFP, which reflect Hepatitis activity, also decreased significantly, similarly to Vs, from baseline to follow-up 12, which was then followed by a plateau.

Marcellin et al. [16], who attempted multiple liver biopsies in patients with SVR after IFN therapy, reported a histologic improvement in inflammation after treatment was completed, but they found no clear evidence of fibrosis improvement even after follow-up for3 years or longer. Therefore, improvement of hepatic fibrosis in the present patients after a short 12 weeks of treatment was not to be expected. The improvement in Vs should be considered to reflect remission of inflammation, rather than improvement in fibrosis.

M2BPGi is a new liver fibrosis marker that quantitatively measures changes in the carbohydrate structure of Mac-2 binding protein [17], and it is also considered useful in predicting carcinogenesis in Hepatitis C patients [18-20]. In this study, M2BPGi, which at baseline was 2.93 C.O.I ± 2.62 C.O.I, or about 3-times the upper normal limit, decreased significantly at EOT to 1.58 C.O.I. ± 1.30 C.O.I. Therefore, it is assumed that elevated M2BPGi, like Vs, is not only due to hepatic fibrosis, but also due to effects caused by inflammation [21].

Only one patient, an elderly man, developed HCC. Baseline ALT and M2BPGi were both markedly high at 113 IU/L and 8.58 C.O.I., respectively, but both decreased significantly at EOT. Vs remained essentially unchanged from 2.06 m/s at baseline to 2.04 m/s at EOT. Vs decreased to 1.82 m/s at follow-up 12, but remained about the same (1.80 m/s) at follow-up 24.

Based on the baseline ALT, Hepatitis seemed to be active before treatment, but histopathology of a surgical specimen showed marked fibrosis with only very mild inflammatory cell infiltration. These results support our previously reported findings that baseline Vs reflects both inflammation and fibrosis [15], whereas Vs at follow-up 12 and later reflects only hepatic fibrosis.

Several studies using TE have reported improvements in liver stiffness with DAA therapy [22-25]. The results of the present study are in agreement with the previously reported data. However, only one study reported by Tada et al. [26] used 2D-SWE. If we hypothesize that liver stiffness, which plateaued 12 weeks after treatment, purely reflects hepatic fibrosis, then Vs at this time point may be a predictor for hepatocarcinogenesis.

Limitations

This study was conducted at a single institution, and although this was a prospective study in which 155 patients were enrolled, data from a smaller number, only 92 patients, could be used for evaluation. Since no patients underwent liver biopsy in this study, the histopathological findings and Vs cannot be compared. In addition, the mean observation period after SVR24 was confirmed was short, only 1.8 years, and only one patient developed HCC. The possibility of Vs after treatment being a predictor for hepatocarcinogenesis is interesting, but further long-term studies in a larger number of patients are needed.

Conclusions

Vs measured using SWE in Hepatitis C patients improved with 12 weeks of DAA therapy. This improvement continued until follow-up 12 (12 weeks after EOT) and then plateaued. The present findings suggest that baseline (before treatment) Vs reflects both hepatic inflammation and fibrosis, whereas Vs at follow-up 12 and later purely reflects hepatic fibrosis.

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