

Observational Study

Changes of shear-wave velocity by interferon-based therapy in chronic hepatitis C

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Abstract

AIM: To evaluate the changes of shear-wave velocity (Vs) by acoustic radiation force impulse after treatment in chronic hepatitis C.

METHODS: Eighty-seven patients with chronic hepatitis C were consecutively treated with combinations of interferon (IFN) plus ribavirin (RBV). Vs value (m/s) was measured with acoustic radiation force impulse before treatment, at end of treatment (EOT), 1 year after EOT, and 2 years after EOT.

RESULTS: In patients with a sustained virological response (SVR) ($n = 41$), Vs significantly decreased at EOT [1.19 (1.07-1.37), $P = 0.0004$], 1 year after EOT [1.10 (1.00-1.22), $P = 0.0001$], and 2 years after EOT [1.05 (0.95-1.16), $P < 0.0001$] compared with baseline [1.27 (1.11-1.49)]. In patients with a relapse ($n = 26$), Vs did not significantly decrease at EOT [1.23 (1.12-1.55)], 1 year after EOT [1.20 (1.12-1.80)], and 2 years after EOT [1.41 (1.08-2.01)] compared with baseline [1.39 (1.15-1.57)]. In patients with a nonvirological response ($n = 20$), Vs did not significantly decrease at EOT [1.64 (1.43-2.06)], 1 year after EOT [1.66 (1.30-1.95)], and 2 years after EOT [1.61 (1.36-2.37)] compared with baseline [1.80 (1.54-2.01)]. Among genotype 1 patients, baseline Vs was significantly lower in SVR patients [1.28 (1.04-1.40)] than in non-SVR patients [1.56 (1.20-1.83)] ($P = 0.0142$).

CONCLUSION: Reduction of Vs values was shown in SVR patients after IFN-plus-RBV therapy by acoustic radiation force impulse.

Key words: Hepatitis C virus; Fibrosis; Interferon and ribavirin; Liver stiffness; Shear-wave velocity

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Core tip: The estimation of the stage of liver fibrosis is important for the prediction of hepatitis outcome, response to treatment, and evaluation of treatment outcomes in patients with chronic liver disease. Methods for noninvasive assessment of liver fibrosis have been developed. Shear-wave velocity (Vs) measured by acoustic radiation force impulse (ARFI) correlate with liver fibrosis stages in various liver diseases. To evaluate Vs value changes measured by ARFI after interferon (IFN) plus ribavirin (RBV) in chronic hepatitis C patients. Reduction of Vs values was shown in sustained virological response patients after IFN-plus-RBV therapy by ARFI.

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INTRODUCTION

Chronic hepatitis C virus (HCV) infection affects approximately 170 million people worldwide^[1]. HCV usually causes chronic infection, which can result in chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma^[2,3]. Therefore, an estimation of the stage of liver fibrosis is important for the prediction of hepatitis outcome, response to treatment, and evaluation of treatment outcomes in patients with chronic liver disease^[4].

The aim of the treatment for chronic hepatitis C is the elimination of the virus. Several studies have shown that sustained virological response (SVR) after antiviral therapy can reduce fibrosis^[5-8]. In addition, partial regression of liver fibrosis has also been reported in patients with nonresponse and relapse to antiviral therapy with pegylated interferon (peg-IFN) and ribavirin (RBV)^[5,6].

Methods of treatment using IFN have continued to advance^[9]. Combination therapy of peg-IFN and RBV with telaprevir, boceprevir, or simeprevir has recently become available^[10-12]. Furthermore, an IFN-free therapy with daclatasvir, asunaprevir, sofosbuvir, ledipasvir, and paritaprevir/ritonavir/ombitasvir plus dasabuvir has also become available^[13-20]. Thus, it is likely that IFN-based therapy will be replaced by IFN-free therapies. The reduction of fibrosis after IFN-free therapies should be evaluated in the future.

To estimate the effect of antiviral therapy, the evaluations of viral load and ALT levels are useful. However, the evaluation of liver fibrosis is also important. Liver biopsy is currently considered the gold standard for assessing the stage of fibrosis in chronic liver disease. However, it is an invasive procedure, with rare but potentially life-threatening complications. In addition, the accuracy of liver biopsy in assessing fibrosis has limitations because of sampling errors and interobserver variability^[21-23].

Methods for noninvasive assessment of liver fibrosis have been developed. Liver stiffness (LS)^[24-32] by transient elastography (TE) with Fibroscan and shear-wave velocity (Vs) measured by acoustic radiation force impulse (ARFI)^[33-37] correlate with liver fibrosis stages in various liver diseases.

The aim of the present study was to evaluate the usefulness of Vs values measured by ARFI for the assessment of liver fibrosis regression after IFN-based therapy.

MATERIALS AND METHODS

Ethical statement

This study was performed in strict accordance with the ethical guidelines of the Declaration of Helsinki and was approved by the ethics committee of Fujita Health University. All study participants provided written

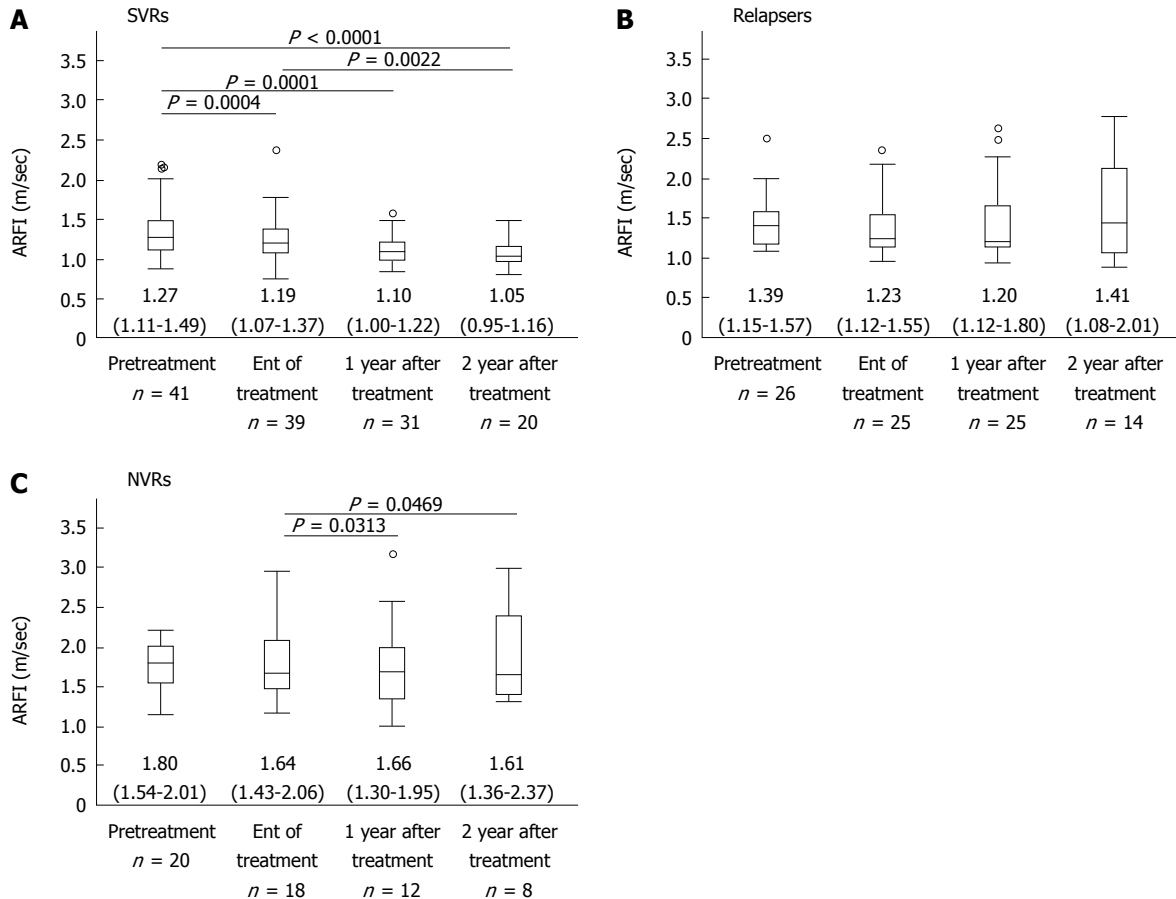


Figure 1 Changes of shear-wave velocity values after interferon plus ribavirin therapy. The shear-wave velocity (Vs) values in the figure were expressed as overall medians. A: In SVR patients, Vs values were significantly lower at EOT [1.19 (1.07-1.36)] than at pretreatment [1.27 (1.11-1.51)] ($P = 0.0004$) in 39 patients in whom Vs values were measured at both points. Vs values were significantly lower at 1 year after treatment [1.10 (1.00-1.23)] than at pretreatment [1.27 (1.11-1.46)] ($P = 0.0001$) in 33 patients in whom Vs values were measured at both points. Vs values were significantly lower at 2 years after treatment [1.05 (0.96-1.16)] than at pretreatment [1.27 (1.11-1.46)] ($P < 0.0001$) in 22 patients in whom Vs values were measured at both points. Vs values were significantly lower at 1 year after treatment [1.07 (0.96-1.17)] than at EOT [1.20 (1.05-1.33)] ($P = 0.0022$) in 20 patients in whom Vs values were measured at both points; B: In patients who relapsed, Vs values did not significantly differ among pretreatment, EOT, 1 year, and 2 years after treatment; C: In patients with NVR, Vs values were significantly higher at 1 year after treatment [1.72 (1.43-2.00)] than at EOT [1.56 (1.25-1.75)] ($P = 0.0313$) in 11 patients in whom Vs values were measured at both points. Vs values were significantly higher at 2 years after treatment [1.58 (1.40-1.66)] than at EOT [1.37 (1.23-1.57)] ($P = 0.0469$) in 7 patients in whom Vs was measured in both points.

informed consent.

Patients

Eighty-seven patients with chronic hepatitis C were consecutively treated with combinations of IFNs and RBV in Fujita Health University Hospital from October 2009 to February 2014 (Table 1).

Seventy patients were treated with peg-IFN- α 2b (1.5 mg/kg per week) and RBV (600-1000 mg/d), 9 patients with peg-IFN- α 2a (180 mg/wk) and RBV (600-1000 mg/d), and 8 patients with IFN- β (1-6 MU/d) and RBV (600-1000 mg/d).

The planned treatment duration was 24, 48, or 72 wk according to HCV genotype, viral load, and response to treatment in the first 12 wk. The responses to IFN therapy were categorized into three types: SVR, where negativity of HCV RNA persisted 6 mo after the end of treatment (EOT); relapse, where HCV RNA became negative during treatment but relapsed to positive after EOT; and nonvirological

response (NVR) where HCV RNA remained positive throughout treatment.

Biological parameters

The biochemical, serological, and virological examinations were performed within 2 d of the Vs measurements: serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, total bilirubin, γ -glutamyl transpeptidase (γ -GTP), alkaline phosphatase (ALP), hyaluronic acid, prothrombin time, platelet count, aminotransferase-to-platelet ratio index (APRI), and fibrosis-4 (FIB-4). APRI values were calculated using the following formula: AST (U/L)/platelets ($10^9/L$) $\times 100$ ^[38]. FIB-4 values were calculated using the following formula: age (years) \times AST (IU/L)/platelets ($10^9/L$) \times [ALT (IU/L)]^{1/2}^[39].

ARFI measurement

Vs measurement by ARFI was performed using a Siemens ACUSON S2000 ultrasound system (Siemens

Table 1 Characteristics of patients studied

	All	SVRs	Relapsers	NVRs	P value
Number of patients	87	41	26	20	
Gender (female/male)	47/40	17/24	20/6	10/10	N.S.
Age (yr)	59 (50-66)	52 (44-63) ²	63 (54-66) ²	62 (51-67)	0.0125 ²
Fibrosis stage (F0-2/F3,4) ¹	38/24	23/4 ³	12/8 ⁴	3/12 ^{3,4}	< 0.0001 ³
Inflammatory grade (A0,1/A2,3) ¹	25/37	14/13 ³	8/12	3/12 ³	0.0154 ⁴
Genotype (1/2) ²	57/28	17/24 ^{2,3,4}	21/4 ^{2,4}	19/0 ^{3,4}	0.0384 ³
					0.0004 ²
					< 0.0001 ³
					0.0281 ⁴
Platelet count ($\times 10^4/\mu\text{L}$)	14.2 (11.7-18.8)	15.7 (12.7-19.5) ³	14.4 (11.4-17.9)	11.1 (9.1-15.7) ³	0.0116 ³
Prothrombin time (%)	97 (91-110)	99 (91-111)	96 (91-110)	97 (88-103)	NS
Albumin (g/dL)	4.2 (4.0-4.5)	4.3 (4.2-4.6) ³	4.2 (3.9-4.5)	4.2 (3.9-4.2) ³	0.0141 ³
Total bilirubin (mg/dL)	0.8 (0.6-1.0)	0.7 (0.5-1.1)	0.7 (0.6-1.0)	0.9 (0.7-1.0)	NS
AST (IU/L)	45 (32-69)	40 (27-59) ³	43 (32-59)	57 (46-88) ³	0.0187 ³
ALT (IU/L)	51 (35-86)	51 (30-75)	47 (33-94)	58 (42-95)	NS
γ -GTP (IU/L)	37 (23-67)	47 (23-83)	28 (21-43) ⁴	44 (27-110) ⁴	0.0205 ⁴
ALP (U/L)	261 (212-345)	244 (208-267) ³	287 (220-389)	358 (223-422) ³	0.0034 ³
Hyaluronic acid (ng/mL)	80 (42-169)	47 (33-94) ³	86 (54-168) ⁴	163 (97-301) ^{3,4}	0.0003 ³
					0.0276 ⁴
HCV RNA (logIU/mL)	6.3 (5.2-6.8)	5.7 (4.8-6.8) ³	6.4 (5.8-6.7)	6.7 (6.3-7.1) ³	0.0109 ³
APRI	0.91 (0.54-1.68)	0.82 (0.40-1.16) ³	0.95 (0.57-1.58)	1.59 (0.85-2.84) ³	0.0083 ³
FIB-4	2.57 (1.66-4.00)	2.04 (1.49-2.70) ^{2,3}	2.95 (2.14-4.49) ²	4.52 (2.82-5.96) ³	0.0108 ²
					0.0001 ³
Vs (m/s)					
Pretreatment	1.36 (1.16-1.72)	1.27 (1.11-1.49) ³	1.39 (1.15-1.57) ⁴	1.80 (1.54-2.01) ^{3,4}	0.0007 ³
					0.0036 ⁴
End of treatment	1.27 (1.12-1.56)	1.19 (1.07-1.37) ³	1.23 (1.12-1.55) ⁴	1.64 (1.43-2.06) ^{3,4}	< 0.0001 ³
					0.0124 ⁴
1 yr after treatment	1.20 (1.06-1.50)	1.10 (1.00-1.22) ^{2,3}	1.20 (1.12-1.80) ²	1.66 (1.30-1.95) ³	0.0192 ²
					0.0013 ³
2 yr after treatment	1.17 (1.03-1.48)	1.05 (0.95-1.16) ^{2,3}	1.41 (1.08-2.01) ²	1.61 (1.36-2.37) ³	0.0096 ²
					0.0004 ³

¹Fibrosis stage, inflammatory grade and genotype performed by a chi square testing; ²Comparison between SVRs and Relapsers; ³Comparison between SVRs and NVRs; ⁴Comparison between Relapsers and NVRs. Data are shown as median (interquartile range). AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; γ -GTP: γ -glutamyltranspeptidase; ALP: Alkaline Phosphatase; APRI: Aminotransferase-to-platelet ratio index; FIB-4: Fibrosis-4; NVR: Non-virological responders; SVR: Sustained virological responder.

Japan Co., Ltd., Tokyo, Japan) before treatment, at EOT (within 6 mo after EOT), 1 year after EOT (7-18 mo after EOT) and 2 years after EOT (19-30 mo after EOT).

The region in the liver to be examined for elastic properties was targeted with a region-of-interest (ROI) cursor while performing B-mode imaging. Tissue at ROI was mechanically excited using acoustic push pulses to generate localized tissue displacements. The displacements resulted in the propagation of the shear wave away from the region of excitation, which was tracked using ultrasonic correlation-based methods. The maximal displacement was estimated for multiple ultrasound tracking beams laterally adjacent to the single push-beam. By measuring the time to peak displacement at each lateral location, the shear wave propagation velocity was reconstructed. The examination was performed on the right lobe of the liver from the right intercostal space. A measurement depth of 2-3 cm below the liver capsule was chosen. Ten successful acquisitions at different locations were

performed on each patient. The results are expressed in meters/second (m/s), and the median value was calculated. The shear wave propagation velocity was considered to be proportional to the square root of tissue elasticity.

The procedures were performed by two investigators (NT and HS) who were blind to clinical, serological and histological data. The correlation in Vs measurement between two operators was satisfactory ($r = 0.934$).

Statistical analysis

Patients were classified according to the responses to IFN plus RBV therapy. Patients with genotype 1 were also examined. The groups were compared by chi-squared test and Mann-Whitney *U*-test. Data were expressed as median and interquartile range.

In the follow-up phase of the study, the significance of changes in Vs values between the pairs of 4 points was evaluated by the Wilcoxon signed-rank test.

The statistical analysis was performed using JMP®

Table 2 Changes of deduced fibrosis stages by interferon plus ribavirin therapy

	SVRs (<i>n</i> = 13)	Relapsers (<i>n</i> = 12)	NVRs (<i>n</i> = 16)
2-point reduction	9 (69.2)	2 (16.7)	0
1-point reduction	2 (15.4)	1 (8.3)	5 (31.3)
No changes	2 (15.4)	6 (50.0)	9 (56.2)
1-point progression	0	3 (25.0)	2 (12.5)
Interval (yr)	2.0 (1.0-2.5)	2.8 (1.7-3.1)	1.6 (0.7-2.4)

SVR: Sustained virological response; NVR: Nonvirological response.

software (SAS Institute, Cary, NC, United States).

RESULTS

Responses to IFN therapy

Forty one of 87 patients (47.1%) achieved SVR, 26 (29.9%) relapsed, and 20 (23.0%) had NVR (Table 1). Age, genotype, and FIB-4 significantly differed between patients with SVR and those who relapsed ($P = 0.0125$, $P = 0.0004$, and $P < 0.0108$, respectively).

Fibrosis stage, inflammatory grade, genotype, platelet count, albumin, AST, ALP, hyaluronic acid, HCV RNA, APRI, and FIB-4 significantly differed between patients with SVR and those with NVR ($P < 0.0001$, $P = 0.0384$, $P < 0.0001$, $P = 0.0116$, $P = 0.0141$, $P = 0.0187$, $P = 0.0034$, $P = 0.0003$, $P = 0.0109$, $P = 0.0083$ and $P = 0.0001$, respectively).

Fibrosis stage, genotype, γ -GTP, and hyaluronic acid significantly differed between patients who relapsed and those with NVR ($P = 0.0154$, $P = 0.0281$, $P = 0.0205$, and $P = 0.0276$, respectively).

Vs values at pretreatment were significantly higher in patients with NVR than in those achieving SVR and those who relapsed ($P = 0.0007$, and $P = 0.0036$, respectively). Vs values at EOT were significantly higher in patients with NVR than those who achieved SVR and those who relapsed ($P < 0.0001$, and $P = 0.0124$, respectively). Vs values at 1 year after EOT were significantly lower in SVR patients than in patients who relapsed and in those with NVR ($P = 0.0192$, and $P = 0.0013$, respectively). Vs values at 2 years after EOT were significantly lower in patients achieving SVR than in patients who relapsed or had NVR ($P = 0.0096$, and $P = 0.0004$, respectively).

Changes of Vs values

In 39 patients achieving SVR whose Vs values were measured at both points, Vs values were significantly lower at EOT [1.19 (1.07-1.36)] than at pretreatment [1.28 (1.11-1.51)] ($P = 0.0004$). Vs values were significantly lower at 1 year after treatment [1.10 (1.00-1.23)] than at pretreatment [1.27 (1.11-1.46)] ($P = 0.0001$) in 33 patients in whom Vs values were measured at both points. Vs values were significantly lower at 2 years after EOT [1.05 (0.96-1.16)] than at

pretreatment [1.25 (0.97-1.47)] ($P < 0.0001$) in 22 patients for whom Vs values were measured at both points. Vs values were significantly lower at 2 years after treatment [1.07 (0.96-1.17)] than at EOT [1.20 (1.05-1.33)] ($P = 0.0022$) in 20 patients for whom Vs values were measured at both points (Figure 1A).

In patients who relapsed, Vs values did not differ significantly among pretreatment, EOT, 1 year, and 2 years after EOT (Figure 1B).

In 11 patients with NVR whose Vs values were measured at both time points, Vs values were significantly higher at 1 year after EOT [1.72 (1.43-2.00)] than at EOT [1.53 (1.28-1.75)] ($P = 0.0313$). Vs values were significantly higher at 2 years after EOT [1.58 (1.33-1.68)] than at EOT [1.37 (1.20-1.64)] ($P = 0.0469$) in 7 patients in whom Vs was measured at both points (Figure 1C).

Changes of fibrosis stages deduced from Vs according to cut-off values for fibrosis stages

Fibrosis stages were deduced from Vs values according to cut-off values for fibrosis stages^[40]. The cut-off value was 1.28 m/s for F2, 1.44 m/s for F3, and 1.73 m/s for F4. The deduced fibrosis stages of the first and the last measurements were compared among patients with the deduced fibrosis stage F3 or F4 at the first measurement (Table 2). Thirteen of 41 (31.7%) SVR patients had deduced stage F3 or F4 at pretreatment. Nine of 13 patients (69.2%) had two point reduction of deduced fibrosis stage at the last measurement during the median observation period of 2 years. Two patients (15.4%) had 1-point reduction. In patients who relapsed, 12 of 26 patients (46.2%) had deduced stage F3 or F4 at pretreatment. Two patients (16.7%) had 1-point reduction of deduced stage during the median observation period of 2.8 years. One patient (8.3%) had 1-point reduction. Three patients (25.0%) had 1-point progression of deduced stage. In patients with NVRs, 16 of 20 (80.0%) patients had deduced stage F3 or F4 at pretreatment. Five of 16 patients (31.3%) had 1-point reduction of deduced stage during the median observation period of 1.6 years. Two patients (12.5%) had 1-point progression of deduced stage.

Factors correlating with the response to IFN plus RBV therapy among patients with genotype 1

Fifty seven patients (23 men, 34 women, median age 59 years; age range 50-66 years) had HCV genotype 1 (Table 3). Seventeen of 57 patients (29.8%) obtained SVR, 40 (70.2%) had non-SVR (21 patients relapsed and 19 patients had NVRs).

Age, fibrosis stage, ALP, hyaluronic acid, FIB-4, and Vs values were significantly lower in patients who achieved SVR compared with patients with non-SVR ($P = 0.0016$, $P < 0.0001$, $P = 0.0053$, $P = 0.0076$, $P = 0.0014$, and $P = 0.0142$, respectively). Albumin was significantly higher in patients with SVR than in those

Table 3 Characteristics of genotype1 patients studied

	All	SVRs	Relapsers and NVRs	P value
Number of patients	57	17	40	
Gender (female/male)	34/23	7/10	25/15	NS
Age (yr)	59 (50-66)	51 (41-58)	62 (54-67)	0.0016
Fibrosis stage (F0-F2 /F3,4) ¹	25/17	12/0	13/17	< 0.0001
Inflammatory grade (A0,1/ A2,3) ¹	16/26	6/6	10/20	NS
Platelet count ($\times 10^4/\mu\text{L}$)	14.0 (10.7-18.3)	15.4 (13.0-19.5)	13.2 (9.4-17.4)	NS
Prothrombin time (%)	99 (91-111)	102 (91-110)	98 (92-112)	NS
Albumin (g/dL)	4.2 (4.0-4.5)	4.4 (4.2-4.6)	4.2 (4.0-4.4)	0.0496
Total bilirubin (mg/dL)	0.8 (0.6-1.0)	0.8 (0.5-1.1)	0.8 (0.6-1.0)	NS
AST (IU/L)	47 (32-71)	38 (28-63)	48 (35-77)	NS
ALT (IU/L)	50 (35-90)	50 (30-92)	52 (36-91)	NS
γ -GTP (IU/L)	33 (22-51)	37 (15-66)	30 (23-50)	NS
ALP (U/L)	267 (212-379)	246 (187-262)	314 (215-416)	0.0053
Hyaluronic acid (ng/mL)	95 (46-173)	51 (21-98)	114 (68-180)	0.0076
HCV RNA (logIU/mL)	6.4 (5.8-7.0)	6.0 (5.2-7.1)	6.4 (6.1-6.9)	NS
APRI	0.91 (0.56-1.69)	0.80 (0.45-1.09)	1.05 (0.63-1.73)	NS
FIB-4	2.69 (1.64-4.46)	1.66 (1.26-2.53)	3.34 (2.23-4.63)	0.0014
Vs (m/s); Before treatment	1.44 (1.17-1.75)	1.28 (1.04-1.40)	1.56 (1.20-1.83)	0.0142

¹Fibrosis stage and Inflammatory grade performed by a χ^2 testing. Comparison between SVRs and non-SVRs (Relapser/NVRs). Data are shown as median (interquartile range). AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; γ -GTP: γ -glutamyltranspeptidase; ALP: Alkaline Phosphatase; APRI: Aminotransferase-to-platelet ratio index; FIB-4: Fibrosis-4; NVR: Non-virological responders; SVR: Sustained virological responder.

Table 4 Logistic regression analysis for predictive factors in interferon plus ribavirin therapy for genotype1 patients

	β	Standard error	P value	95%CI
Age (yr)	-0.347	0.006	0.008	-0.0271-(-0.0043)
ALP (U/L)	-0.196	0.001	NS	-0.0021-(-0.0003)
Vs (m/s)	-0.196	0.162	NS	-0.5773-(-0.0721)

Vs: Velocity of shear wave; ALP: Alkaline phosphatase.

with non-SVR ($P = 0.0496$).

In multivariate analysis, age ($P = 0.0077$) was found to be associated with SVR of IFN plus RBV therapy (Table 4).

DISCUSSION

The present study examined the usefulness of Vs values measured by ARFI for the assessment of liver fibrosis change after IFN-plus-RBV therapy. It was demonstrated that Vs values were significantly reduced at EOT and 1 year after EOT in SVR patients compared with pretreatment values, and that Vs values were significantly reduced 2 years after EOT compared with pretreatment values and the values at EOT in patients who achieved SVR. Thus far, several studies with paired pre- and post-IFN therapy biopsies reported decreased fibrosis in 29% (mean times between biopsies, 1.6 years)^[41], 44% (2.5 years)^[42], 59% (3.7 years)^[43] or 82% (5.2 years)^[7] of patients with SVR. George *et al*^[7] reported that 67% of patients with SVR and pretreatment cirrhosis or advanced fibrosis had a 2-point or greater decrease in the fibrosis score in 5.2 years. In the present study, 9 of 13 patients (69.2%) had a 2-point reduction of deduced fibrosis

stage in a period of 2 years. Two of 13 patients (15.4%) had a 1-point reduction. Our previous study using TE demonstrated that 78% of SVR patients with pretreatment-deduced fibrosis stage F3 or F4 had a 2-point or greater decrease in deduced fibrosis stage in a period of 2.1 years^[44]. The occurrence rates and the degree of fibrosis reduction after IFN-based treatment in the present study with ARFI were comparable with our previous study with TE and were higher than the reports based on liver biopsy. The reason for higher occurrence rates and degree of fibrosis reduction after IFN-based treatment with ARFI and TE may be attributed to the higher sensitivity of ARFI and TE to detect subtle reduction of fibrosis compared with liver biopsy.

The reduction of Vs value observed in the present study is probably the reflection of fibrosis regression. Several studies with TE, another noninvasive method for the assessment of liver fibrosis, have reported that LS is affected by ALT levels. Fraquelli *et al*^[45] reported that, by TE, fibrosis staging is overestimated by necroinflammatory activity and steatosis. Coco *et al*^[46] found that LS is higher in patients with an elevated ALT than in those with either spontaneous biochemical remission or after antiviral therapy. Thus, it is probable that ALT or inflammatory activity affects TE. Our previous study demonstrated that Vs is not affected by inflammatory activity. Rizzo *et al*^[47] reported that ARFI was not associated with ALT, body mass index, Metavir score, and liver steatosis, while TE was significantly correlated with the ALT value by multivariate analysis. Bota *et al*^[48] reported that discordance of at least two stages of fibrosis between ARFI results and histologic assessments were associated: female sex ($P = 0.004$), interquartile range interval (IQR) $\geq 30\%$, high ALT,

and high AST in an univariate analysis, while in a multivariate analysis, female sex and IQR of $\geq 30\%$ were associated with discordances. However, Yoon *et al.*^[49] reported that the optimum cut-off values for Vs measured by ARFI were 1.13 m/s for F2 or more and 1.98 m/s for F4; these decreased to 1.09 m/s for F2 or more and 1.81 m/s for F4 in patients with normal ALT levels. Thus, the faster and conspicuous reduction of Vs may be partially attributed to the reduction of inflammatory activity. Further studies are necessary to elucidate the correlation of reduction of Vs values with histological changes after SVR.

Among patients who relapsed, there were no significant changes in Vs value among the points of ARFI measurement. In NVR patients, the Vs values did not change from pretreatment to EOT, although they increased from EOT to 1 year after EOT and 2 years after EOT. These findings indicate that there was no significant improvement of fibrosis in patients who relapsed and that fibrosis progressed in NVR patients after IFN-based therapy. The deduced fibrosis stages progressed in 25% of patients who relapsed and in 12.5% of patients with NVR whose pretreatment-deduced stages were F3 or F4. In the patients with pretreatment-deduced stages of F0-2, the deduced fibrosis stage increased one point or more in 28.6% of patients who relapsed and 50% of those with NVR (data not shown).

In our previous study using TE, LS significantly reduced at EOT and at 1 year after EOT compared with baseline among those who relapsed. This finding may indicate that the inflammatory activity increases LS values of TE. In the present study using ARFI, Vs was not significantly reduced in patients who relapsed. This may indicate that the inflammatory activity does not affect Vs values of ARFI. Therefore, ARFI may be a more appropriate method for the follow-up of fibrosis regression after antiviral treatment compared with TE.

In patients with HCV genotypes 2 or 3, the combination of peg-IFN and RBV is usually given for 24 wk, achieving rates of SVR of approximately 75%-85%. In patients with HCV genotype 1, the combination of peg-IFN and RBV is usually given for 48 weeks, resulting in SVR rates of 40%-50%^[50,51]. The fibrosis stage has been reported to be one of the predictive factors for SVR in HCV genotype 1. In the present study, baseline Vs was significantly lower in patients achieving SVR than in those who relapsed or had NVR. However, in multivariate analysis, age was identified as the only risk factor associated with SVR. In a previous study, older age was reported to decrease the SVR rate of IFN plus RBV therapy^[52].

In the present study, there was a reduction of Vs values in patients who achieved SVR after IFN plus RBV therapy. However, IFN-free therapy has become the first-line therapy for chronic hepatitis C. In the same fashion, there is an ongoing study to determine the changes of Vs values during IFN-free therapy to then evaluate the changes of fibrosis after IFN-free

therapy in our hospital.

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COMMENTS

Background

Interferon (IFN) treatment has been demonstrated to reduce liver fibrosis by liver biopsies and by transient elastography which can assess liver fibrosis noninvasively. The shear-wave velocity (Vs) by acoustic radiation force impulse (ARFI) is another noninvasive method for assessing liver fibrosis. Reduction of liver fibrosis after antiviral therapy has not been well evaluated by ARFI.

Research frontiers

The Vs value by ARFI is a brand-new ultrasound technology. Since the invention of ARFI, a lot of studies demonstrated that ARFI is a useful tool to evaluate liver fibrosis in chronic liver diseases noninvasively.

Innovations and breakthroughs

The present study evaluated Vs value by ARFI before and after IFN treatment and demonstrated the reduction of liver fibrosis after IFN treatment in SVR patients with chronic hepatitis C.

Applications

This research showed that ARFI is a useful tool to evaluate the reduction of fibrosis in patients with chronic hepatitis C after IFN-plus-RBV therapy.

Terminology

The Vs value measured by acoustic radiation force impulse is a new ultrasonography modality to evaluate liver stiffness by acoustic radiation force-based imaging method. The examiners can choose the place where Vs value is measured on the conventional B-mode ultrasound image.

Peer-review

The article is a well-designed and performed work on the changes of shear wave velocity in patients with chronic hepatitis C who received antiviral treatment. The Vs values were significantly reduced at EOT and at different time points post treatment in patients with SVR while no changes were identified in patient with treatment failure.

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