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Low Pretreatment Acoustic Radiation Force Impulse Imaging (ARFI) Values Predict Sustained Virological Response in Antiviral Hepatitis C Virus (HCV) Therapy

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Non-invasive procedures such as acoustic radiation force impulse imaging (ARFI) shear-wave elastography are currently used for the assessment of liver fibrosis. In the course of chronic hepatitis C, significant liver fibrosis or cirrhosis develops in approximately 25% of patients, which is a negative predictor of antiviral treatment response. Cirrhosis can be prevented by successful virus elimination.
In this prospective study, a pretreatment ARFI cutoff value of 1.5 m/s was evaluated in relation to sustained virological response to anti-HCV therapy.

Material/Methods: In 23 patients with chronic hepatitis C, liver stiffness was examined with ARFI at defined times before and under antiviral triple therapy (peginterferon, ribavirin in combination with a first-generation protease inhibitor, and telaprevir or boceprevir). Patients were stratified into 2 groups based on pretreatment ARFI values (<1.5 m/s and ≥1.5 m/s) for the assessment of virological response.

Results: The liver stiffness at baseline for all patients was 1.57±0.79 m/s (ARFI median ± standard deviation; margin: 0.81 m/s to 3.45 m/s). At week 4 of triple therapy, patients with low pretreatment ARFI values had higher rates of HCV-RNA negativity (69% *vs.* 43%), reflecting an early rapid virological response (eRVR). Sustained virological response (SVR) was found in 75% (12/16) of patients with an ARFI value <1.5 m/s and only 57% (4/7) of patients with ARFI value ≥1.5 m/s.

Conclusions: Patients with chronic hepatitis C and pretreatment ARFI <1.5 m/s showed earlier virus elimination and better response to treatment.

MeSH Keywords: Decision Support Techniques • Elasticity Imaging Techniques • Hepatitis C Antibodies

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Background

Non-invasive shear-wave elastography techniques to determine the fibrosis stage of the liver, such as transient elastography (TE) with Fibroscan and acoustic radiation force impulse (ARFI) have found their way into the standard diagnostics of chronic liver diseases [1–4]. Shear-wave elastography techniques measure liver stiffness, which correlates well with histological stage of liver fibrosis [1,3,5,6]. With these techniques it is possible to distinguish between mild liver fibrosis *vs.* severe liver fibrosis or cirrhosis [3,5,7]. Fibrosis plays an important role in chronic liver diseases, especially in chronic hepatitis C infection, because advanced liver fibrosis is a negative predictor of response to antiviral therapy [8]. Thus, high pretreatment shear-wave elastography values may be a negative predictor of successful virological response to therapy [9].

We used the ARFI technique instead of TE to measure liver elastography values before, during, and after treatment of chronic hepatitis C infection. The ARFI technique is an established ultrasound-based shear-wave elastography technique. ARFI is integrated into a conventional ultrasound (US) machine; therefore, measurements are performed under direct B-mode visualization of the liver parenchyma [10]. ARFI presents an alternative method to TE, which has some limitations. TE is dedicated to specific equipment not included in an US machine; measurements are based on M- and A-mode imaging, but no B-mode information is available. TE is limited in patients with severe obesity and impossible in patients with ascites [11]. With the ARFI technique, B-mode information can be obtained and shear-wave elastography can be performed quickly using the same device [3,12]. The US-guided device makes it possible to identify the most appropriate place for the elastographic measurements and thereby enables valid results to be achieved in most patients [13]. Therefore, ARFI has a higher rate of reliable measurements and diagnostic efficacy comparable to TE in detecting significant liver fibrosis [14–16].

ARFI involves targeting of an anatomic region to be interrogated for elastic properties with a region of interest (ROI) curser during B-mode imaging. A short ARFI is generated by an ultrasound transducer causing localized tissue displacement, which leads to a lateral shear-wave. Shear-wave velocity (SWV) is tracked by ultrasound, which is proportional to the square root of tissue elasticity [14]. In 2 meta-analyses, ARFI values had good correlation to liver fibrosis assessed by histology [6,10].

In chronic hepatitis C infection, ARFI values are correlated with fibrosis stage [9,17,18]. The grade of liver inflammation is not reflected by elastography in chronic hepatitis C infection in contrast to chronic hepatitis B infection. ARFI values in chronic hepatitis B infection are influenced by fibrosis and inflammation [19–21]. In a previous study, we defined a cutoff ARFI SWV of 1.5 m/s, distinguishing between no/mild and severe fibrosis in chronic hepatitis C patients [2]. In the current study we evaluated ARFI values in patients with chronic hepatitis C undergoing antiviral therapy.

Treatment of chronic hepatitis C (HCV) is currently undergoing major changes due to the use of direct antiviral active substances (DAA), with significantly higher rates of virological response. The first substances in this group were telaprevir and boceprevir, given in combination with pegylated alpha interferon (IFN) and ribavirin. Complete IFN-free treatment regimens are available [22] but some countries still commonly use IFN-containing regimens, such as combinations with telaprevir or boceprevir, for socio-economic reasons [23,24]. Although these therapies can significantly increase the virological response in contrast to dual therapy with PEG-IFN alpha/ribavirin, they have a significantly worse adverse effects profile compared to dual therapy. Therefore, it is important to identify predictive factors for treatment response, such as the IL28B polymorphism in HCV genotype 1, at an early stage of therapy to be able to adjust therapy accordingly [25]. For example, a Japanese study showed that patients with higher shear-wave velocities (ARFI) and an unfavorable IL28b genotype had significantly lower sustained virological response rates (SVR) [26]. The aim of the present prospective study was to evaluate the cutoff ARFI shear-wave velocity of 1.5 m/s in antiviral HCV treatment with PEG-IFN, ribavirin, and first-generation DAA as a prognostic marker of treatment response.

Material and Methods

Patients

We included all daily routine patients with chronic hepatitis C from the outpatient clinic of Medical Department 1, University of Erlangen, if they had received 1 of these 2 therapies. Between September 2012 and April 2014, patients with HCV genotype 1 who started antiviral treatment were recruited for the study prior to treatment during their initial visit. Prior to patient enrollment, the local Ethics Committee (University of Erlangen) approved the project. Patients were asked to undergo additional assessment by ARFI elastography. A total of 23 patients were considered for further evaluations. Written informed consent was obtained from all patients. Descriptive data (gender, age, BMI, history of HCV infection, prior therapies), and blood test results (HCV-RNA, IL28b, total bilirubin, AST, ALT, γ-GT, AP, albumin, leukocytes, and platelet count) were evaluated (Table 1). B-mode liver US was performed prior to ARFI by 2 experienced sonographers with more than 5-year experience in US (German Society of Ultrasound in Medicine (DEGUM) – Level 2 and 3). Patients were divided into 2 groups according to their pretreatment ARFI value (no/mild fibrosis

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Table 1. Patient baseline characteristics.

	All patients (n=23)	<1.5 m/s (n=16)	≥1.5 m/s (n=7)	significance (p) </≥1.5 m/s
Pretreatment ARFI value [<1.5m/s/≥1.5m/s]	[16/7]	[16/0]	[0/7]	
gender [m/f]	[17/6]	[12/4]	[5/2]	n.s.
age [years]	50.39±10.67	56.08±10.23	47.14±11.74	n.s.
BMI [kg/m^2]	26.7±4.9	25.58±2.24	30±5.03	0.0074
Previous treatment [naive/experienced]	[10/13]	[8/4]	[2/5]	n.s.
Il 28b [TT/TC/CC]	[2/12/9]	[2/8/6]	[0/4/3]	n.s.
HCV RNA [IE/ml]	2.989.421±3.821.878	2.691.429±3.591.168	3.823.800±4.757.707	n.s.
AST [U/l]	71.91±57.02	50.27±19.8	118.29±82.36	0.0044
ALT [U/l]	78.05±48.86	65.53±33.57	104.86±67.05	n.s.
Gamma-GT [U/l]	99.23±75.96	89.27±81.62	120.57±62.2	n.s.
Bilirubin [mg/dl]	0.7±0.33	0.69±0.36	0.7±0.26	n.s.
Albumin [g/l]	43.4±3.93	45±1.68	39.94±5.21	0.0018
Thrombocytes [/nl]	185±60.02	192.6±54.01	168.71±73.15	n.s.
Leucocytes [/nl]	7.49±1.998	7.8±2.03	6.82±1.88	n.s.
Hemoglobin [g/dl]	14.9±1.92	15.27±1.3	14.25±2.85	n.s.
International Normalized Ratio (INR)	1.1±0.1	1.3±0.2	1.2±0.2	n.s.
Median ARFI-value	1.57±0.79	1.18±0.204	2.66±0.86	0.0001
Average	1.61±0.81	1.21±0.19	2.66±0.9	0.0001
IQB	0.28±0.23	0.22±0.13	0.46±0.33	
Genotype [1a/1b]	[9/14]	[4/8]	[1/6]	n.s.
Overall responder [responder/non-responder]	[16/7]	[12/4]	[4/3]	n.s.

Significant differences between patients with initial shear-wave velocities </≥1.5 m/s were observed for BMI, GOT, albumin, and initial shear-wave velocities. n.s. – non-significant.

<1.5 m/s; severe fibrosis >1.5 m/s) to investigate their treatment response.

Patients received 1 of the 2 treatment regimens (boceprevir *vs.* telaprevir) without randomization. Eleven patients received antiviral treatment with PEG-IFN alpha 2a (180 micrograms/week s.c.)/ribavirin (<75 kg: 1000 mg/d; ≥75 kg 1200 mg/d) in combination with boceprevir (800 mg every 8 h). Boceprevir was started after a 4-week lead with PEG-IFN/ribavirin as specified by the label.

The other 12 patients received peginterferon alpha 2a (180 micrograms/week s.c.)/ribavirin (<75 kg: 1000 mg/d; ≥75 kg 1200 mg/d) in combination with telaprevir (750 mg every 8 h) without lead-in. In both therapy regimens, dose modifications of peginterferon or ribavirin were made according to the label in case of adverse events. Duration of therapy was 24 to 48 weeks, depending on pretreatment outcome, virological response, and presence of cirrhosis, according to the drug label of boceprevir and telaprevir. Sustained virological response was defined as RNA viral load <10 U/l (Abbott RealTime HCV) 24 weeks after end of treatment.

ARFI assessment

ARFI is a device integrated into a conventional US system. Elastometry can be performed during real-time B-mode US with a single transducer in the Acuson S2000 US system (Virtual TouchTM Tissue Quantification, Siemens Acuson S2000, Siemens Medical Solutions, Erlangen, Germany). A quadratic

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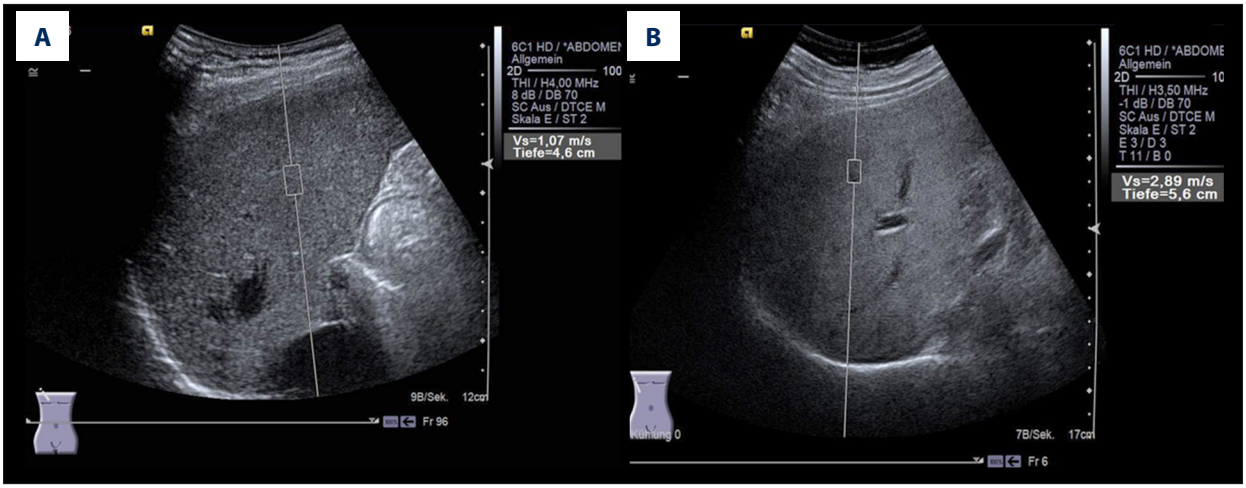

Figure 1. Example of ARFI measurement: During real-time B-mode US, a region of interest (10×5 mm) is placed in the liver parenchyma (segment VII). *Vs.* (shear-wave velocity): 1.07 m/s which represents no significant fibrosis (**A**); 2.89 m/s which represents significant fibrosis/cirrhosis (**B**).

cursor with a size of 10x5 mm representing the anatomic ROI to be measured is placed in the selected area of the liver parenchyma (Figure 1). At the push of a button, a short-duration acoustic pulse is transmitted, which leads to localized tissue displacement and consecutive shear-wave propagation away from the area of excitation. The shear-wave propagation velocity (expressed in m/s) is proportional to the square root of tissue elasticity within the cursor [14,27]. All patients in our study were in the fasting state (at least 2 h after a meal) and were performing relaxed breathing arrest. ARFI imaging was performed on the day of clinical examination and blood withdrawal, with an Acuson S2000 US system curved-array transducer (6C1HD; 4 MHz). Ten valid measurements in the right (segment VII) hepatic lobe using an intercostal approach were made in all patients, avoiding large vessels and bile ducts [28]. The duration of all ARFI measurements was approximately 5–10 min. For the assessment of liver stiffness, the median of 10 valid ARFI measurements was calculated with an interquartile range (IQR) <30% as a control for valid results. ARFI measurements were performed for each patient at the following time points: before therapy, week 4, 12, 24, and 48 of triple therapy, and 24 weeks after end of therapy (SVR). This means that patients in the boceprevir group received the second measurement at week 8 of treatment (4-week lead-in and 4-week triple-therapy.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (Version 19.0.0.1, IBM SPSS statistics, NY). Clinical and laboratory data of the patients and ARFI-values are expressed as mean ± standard deviation (SD), counts, and percentages, as appropriate. Continuous variables of independent groups were calculated with the *t* test. Non-parametric tests were chosen to compare median values of 2 independent samples by Mann-Whitney U test in non-normally distributed data. All tests were 2-sided. A p-value <0.05 indicated a significant correlation or difference.

Results

Baseline characteristics of patients

The overall study population of 23 patients consisted of 17 males (74%) and 6 females (26%). Fourteen patients (61%) had HCV genotype 1b and 9 patients (39%) had genotype 1b. Thirteen patients (57%) were treatment-experienced with peginterferon/ribavirin and were non-responders or relapsers. The mean age was 50.4±10.7 years, and the BMI value was 26,7±4,9 kg/m^2 (Table 1). The median shear-wave velocity value according to pretreatment ARFI measurements was 1.57±0.79 m/s. Patients were stratified according to pretreatment ARFI values defining by a cutoff ARFI shear-wave velocity of 1.5 m/s distinguishing between no/mild and severe fibrosis [2]. Group A was defined by pretreatment ARFI values <1.5 m/s (n=16) and group B by ≥1.5 m/s (n=7). Two patients in the ARFI ≥1.5 m/s group stopped at week 4 of triple therapy due to nonresponse. At week 12 of triple therapy, 4 more patients stopped therapy as a consequence of nonresponse (1 patient <1.5 m/s, 3 patients ≥1.5 m/s at day 0). Therapy was shortened to 24 weeks of triple therapy in 17 patients (<1.5 m/s n=12 of 16; ≥1.5 m/s n=5 of 7) because of early virologic response (HCV-RNA-negative at week 12 of triple therapy).

Virological response in relation to ARFI measurement:

Sixteen out of 23 patients presented negative HCV-RNA 24 weeks after end of treatment (SVR), corresponding to an

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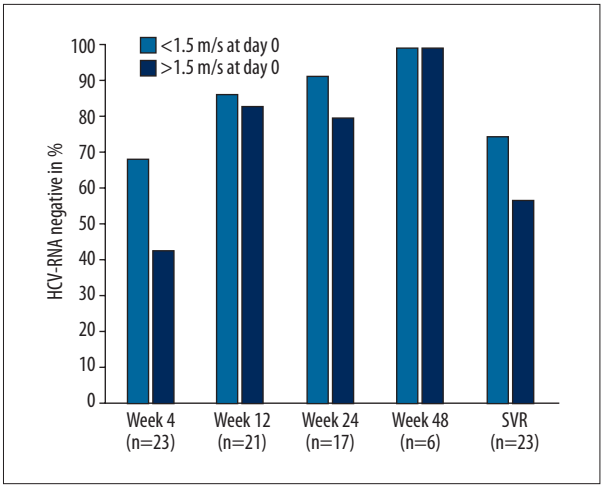

Figure 2. A low baseline shear-wave velocity <1.5 m/s (n=16) results in a higher percentage of HCV-RNA negativity at week 4 of triple therapy (69% *vs.* 43%, p=0.363; n.s. (non-significant)) and 24 weeks after end of therapy (75% *vs.* 57%, p=0.6258; n.s.) compared to high baseline shear-wave velocity (≥1.5 m/s) (n=7). During therapy, no differences in HCV-RNA negativity were observed between groups (A <1.5 *vs.* B ≥1.5 m/s: week 12: group A 87% *vs.* group B 83%; week 24: 92% *vs.* 80%; week 48 100% *vs.* 100%; all n.s.).

overall SVR rate of 69.6% (SVR Boceprevir-regimen: 63.6%; SVR Telaprevir-regimen: 75%). Patients with low pretreatment shear-wave velocity <1.5 m/s (group A) presented a higher percentage of HCV-RNA negativity at week 4 of triple therapy (69% *vs.* 43%) and 24 weeks after end of therapy (75% *vs.* 57%) compared to patients with high pretreatment shear-wave velocity (≥1.5 m/s) (group B) (Figure 2). During therapy, HCV-RNA negativity were approximately the same in both groups, with no significant differences in HCV-RNA negativity (week 12: group A 87% *vs.* group B 83%; week 24: 92% *vs.* 80%; week 48 100% *vs.* 100%). Due to the small number of cases, no significant differences were found. However, clear trends could be identified at week 4 of treatment and at 24 weeks after treatment (SVR).

Discussion

In the present study, low pretreatment shear-wave elastography values (ARFI <1.5 m/s) were found to be a predictor of successful antiviral HCV treatment with peginterferon-based triple-therapy. Predictive factors for sustained virological response (SVR) are essential because of a variety of adverse events. Most predictive factors are known from dual therapy without DAA. Thus, a low initial viral load, a favorable IL28b genotype (CC), lower BMI, absence of cirrhosis, genotype 1b, and an early rapid virological (eRVR) are important prognostic factors of SVR in triple therapy with telaprevir or boceprevir [8,25]. These therapeutic regimens are not the therapeutic standard in Western countries, but are still in use as antiviral HCV-therapies in a variety of countries with lower health-care budgets, such as Eastern European countries4[24]. Furthermore, in dual therapy with pegylated interferon and ribavirin, elastography value was shown to be a significant predictor of antiviral response to peginterferon/ribavirin in HCV treatment [26].

HCV patients with higher ARFI values have lower rates of response to IFN-based therapy [9]. This observation is partly explained by a higher fibrosis stage. Higher-grade fibrosis is associated with a worse virological response to IFN-containing therapies [8,29].

ARFI is established in diagnosis of liver fibrosis [6,12]. The diagnostic accuracy of ARFI quantified by AUROC was 87% for the diagnosis of significant fibrosis, 91% for the diagnosis of severe fibrosis, and 93% for the diagnosis of liver cirrhosis. A diagnostic tool is defined as perfect if the AUROC is 100%, excellent if the AUROC is greater than 90%, and good if it is greater than 80% [30,31]. According to these results, ARFI can be used in clinical practice as a good tool for the diagnosis of significant fibrosis and as an excellent tool for the diagnosis of severe fibrosis and liver cirrhosis [10]. In a meta-analysis of 8 studies including 518 patients with a variety of liver diseases, an ARFI cutoff value of 1.55 m/s was defined for F3 fibrosis in histology [10]. In a previous study, a cutoff shear-wave velocity of 1.5 m/s, which differentiates between a low (F0–F2) and a higher-grade (F3–F4) fibrosis in the subgroup of HCV patients, was assessed. Thus, we investigated the current patient collective in terms of ARFI values and the virological response with a cutoff of 1.5 m/s [2]. The group with a pretreatment shear-wave velocity <1.5 m/s had a higher proportion of HCV-RNA-negative patients at week 4 of triple therapy and 24 weeks after end of treatment (SVR 24) compared to those with shear-wave velocity of ≥1.5 m/s. During the remaining period of therapy, the proportion of HCV-RNA negative patients was approximately the same in both groups.

Week 4 of triple therapy is a hallmark in these HCV therapeutic regimens. If patients are negative after 4 weeks of antiviral therapy with telaprevir or 8 weeks with boceprevir (week 4 of triple therapy), nearly 90% achieve SVR. This early rapid virological response (eRVR) is a very strong predictor of SVR [8]. Thus, our pretreatment ARFI values reflect the virological response at week 4 (eRVR) with more HCV-RNA-negative patients in our group A (pretreatment ARFI value <1.5 m/s). This enables prognosis of virological response in the early phase of therapy without waiting for laboratory results. This could be important in case of strong adverse events and the pending decision of therapy discontinuation.

At 24 weeks after end of therapy (SVR 24), we noticed a significant difference in HCV-RNA-negativity between the 2 groups

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(shear-wave velocity ≤/>1.5 m/s), with higher SVR rates in patients with lower initial shear-wave velocities. These findings agree with data from dual therapy, in which significantly lower ARFI values were found in case of SVR [9].

Limitations

We acknowledge that possible patient selection bias, misclassification or information bias, and the small number of patients analyzed might impact the veracity of the results of our study, especially significance levels. Nevertheless, our study shows a clear indication that an ARFI cutoff value of <1.5 m/s is a strong indicator for SVR in IFN-based triple therapy of HCV.

Conclusions

This pilot study evaluated the usefulness of pretreatment ARFI shear-wave elastography for rapid data assessment reflecting virological response during antiviral triple therapy with boceprevir and telaprevir. Therefore, a low initial shear wave velocity <1.5 m/s in ARFI is a prognostic factor of SVR in these therapy-regimes. Further evaluation of ARFI in this clinical context with larger number of patients is needed to verify our results. This was not feasible for us because second-generation DAA is now used in Germany.

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