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Changes in graft stiffness after effective treatment of recurrent hepatitis C in liver transplant recipients during long-term follow-up

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Abstract

Background. *The main mechanism underlying the progression of chronic liver transplant disease is an increase in fibrosis, which is associated*

with an increase in liver stiffness. An effective antiviral therapy for recurrent hepatitis C has led to the increased graft and recipient survival rates.

***Objective**. To study the long-term effect of successful antiviral therapy on changes in the graft fibrosis stage in liver transplant recipients with recurrent hepatitis C.*

***Material and methods**. Transient elastography was used to study the change in liver stiffness in 33 liver transplant recipients with recurrent hepatitis C before the start of antiviral therapy and 54 months (IQR: 37;59) after its completion. The median liver stiffness values before antiviral therapy and at the end of follow–up were 7.8 kPa (IQR: 6.1;12.0), and 6.4 kPa, respectively (IQR: 5.5; 7.7; p<0.0001). Upon completion of the follow–up, the fibrosis stage decreased by 2 in 4 (12.1%) recipients, by 1 in 8 (24.2%) recipients. In 19 (57.6%) cases, the stage of fibrosis did not change, and in 2 (6.1%) recipients it increased by 1. No clear correlations were found between any of the following parameters: alanine aminotransferase activity, gamma-glutamyl transpeptidase activity, body mass index and the liver stiffness assessed before the start of antiviral therapy and on follow-up completion.*

***Conclusion**. Effective antiviral therapy leads to a long-term (over 4-5 years) decrease in liver stiffness, which is largely due to the slowdown and reverse progression of liver fibrosis. The effect of non-HCV-related risk factors on liver stiffness in this patient population is not significant.*

Keywords: liver stiffness, transient elastography, liver transplantation, recurrent hepatitis C, antiviral therapy

Conflict of interests Authors declare no conflict of interest

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ALT, alanine aminotransferase
AVT, antiviral therapy
BMI, body mass index
CI, confidence interval
DAA, direct acting antiviral drug
GGTP, γ-glutamyl transpeptidase
HCC, hepatocellular carcinoma
IQR, interquartile range
LS, liver stiffness
LT, liver transplantation
SVR, sustained virologic response
TE, transient elastography
ThE, thromboelastometry

Introduction

The main mechanism underlying the progression of chronic liver diseases, including hepatitis C (HCV), with the development of decompensated cirrhosis, is the increase in fibrosis followed by structural reorganization of the organ. HCV infection reoccurs in the first months after liver transplantation (LT) in all recipients in whom the viral RNA was detected in blood at the time of LT. The rate of fibrosis progression significantly accelerates in immunosuppressive therapy in liver recipients with recurrent hepatitis C.

The standard method for assessing liver fibrosis is histological examination. Liver biopsy is associated with the risk of complications and has a number of limitations due to its invasive nature [1–3]. In addition, the severity of fibrosis in different fragments of liver tissue obtained during biopsy varies [4].

Recently, non-invasive methods have become widely used to determine the stage of fibrosis in patients with chronic liver diseases.

These methods include a number of calculated parameters based on the determination of biomarkers in blood [5], and an instrumental assessment (ultrasound or magnetic resonance imaging) of the liver stiffness (LS), i.e. elastography. The most common and well-validated elastography method in immunocompetent patients is a shear wave elastography (transient elastography (TE) to measure the liver stiffness by the Fibroscan device; Echosense, Paris, France) [6]. The clinical significance of measuring LS by TE during antiviral therapy (AVT) and during subsequent long-term monitoring of recipients with recurrent hepatitis C remains poorly understood.

The objective was to study the long-term impact of effective antiviral therapy on the changes in liver transplant fibrosis stages in patients with recurrent hepatitis C.

Material and methods

We studied changes in LS in 33 liver transplant recipients with recurrent hepatitis C before the start of AVT and some time after its completion. Twenty-two men and 11 women were examined; the mean age at the time of the first examination was 54.2 years old (95% confidence interval (CI) [51.6–56.8]). Liver transplantation was performed for liver cirrhosis resulting from chronic hepatitis C (in combination with hepatocellular carcinoma in 10 cases). No cases of HCC progression were observed during the follow-up period. In two cases, the recipients had received a liver fragment from a living related donor; in the remaining cases, the whole graft had been obtained from a deceased donor. All patients received maintenance immunosuppressive therapy with either tacrolimus (n=27) or cyclosporine (n=6), of whom 19 patients received dual immunosuppression with everolimus and a reduced dose of tacrolimus (n=16) or cyclosporine (n=3).

Thirty-one patients received direct-acting antiviral therapy for 12 or 24 weeks. In two cases, the therapy included pegylated interferon, sofosbuvir and ribavirin. All patients achieved a sustained virologic response (SVR).

All recipients underwent LS measurement using transient elastography (*FibroScan*-502, *Echosens*, France) before the start of AVT and again at different time-points after its completion. In case there were several measurements performed after the AVT completion, the value obtained at the longest term was used for analysis. The examination was performed by two certified specialists (A.R. Niyazov, K.Yu. Burtsev) using a standard technique. At the time of examination, alanine aminotransferase (ALT) and γ-glutamyl transpeptidase (GGTP) activities were determined, and the body mass index (BMI) was calculated.

The stage of graft fibrosis based on the results of TE was classified according to B. Della-Guardia et al. (2017): the cut-off being 8.1 kPa for stage 1 fibrosis (F1); 12.3 kPa for stage 2 fibrosis (F2); 16.5 kPa for stage 3 fibrosis (F3), and 17.6 kPa for stage 4 fibrosis (F4) [7].

Statistical processing of digital values was performed using the Statistica 14.0 software (StatSoft, Inc., USA). The results are presented as the mean and 95% CI for variables with a normal distribution; and as the median and interquartile range (IQR) for quantitative variables with a distribution different from normal. Spearman's correlation analysis was used to assess the relationship between quantitative variables. The statistical significance of differences between the compared values when comparing two related groups was determined using the Wilcoxon test. Differences were considered statistically significant at p value being lower than 0.05.

Results

At the time of making the analysis, all recipients were alive. The median follow-up period between measurements was 58 months (IQR 44;72). The median follow-up period between the start of AVT and the last measurement was 54 months (IQR 37;59), the median follow-up period between the first measurement point and the start of AVT was 4.5 months (IQR 1.4;7.6). The median follow-up from LT to the start of AVT was 24 months (IQR 10; 44).

The median LS before AVT was 7.8 kPa (IQR 6.1;12.0), the median LS on follow-up completion was 6.4 kPa (IQR 5.5;7.7), p<0.0001, statistically significant (Figure).

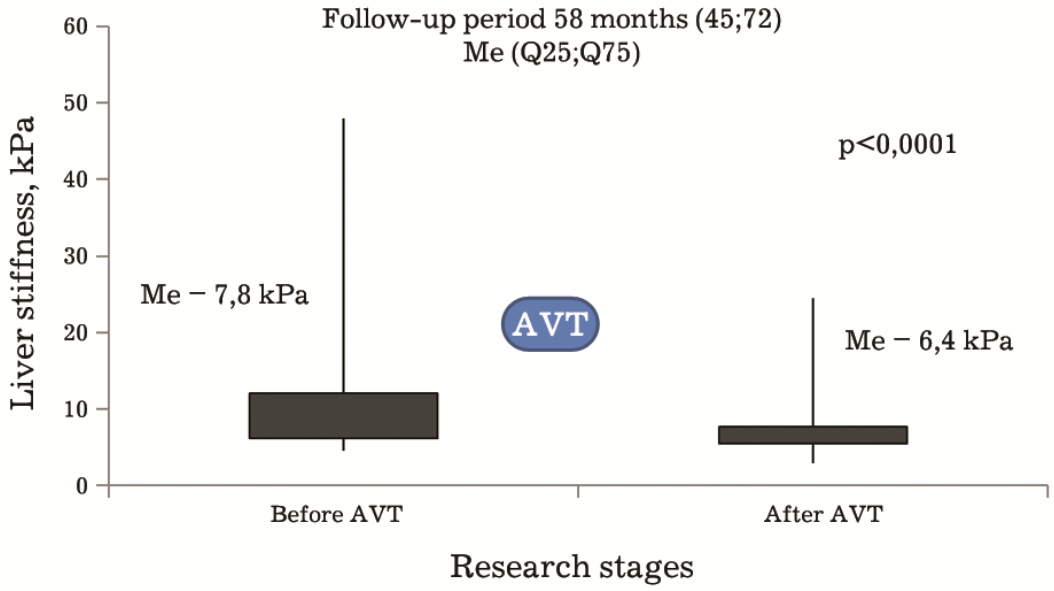

Figure. Changes in liver graft stiffness after effective antiviral therapy in 33 recipients

The change in the stages of liver fibrosis before AVT and on follow-up completion is presented in the table.

Table. Liver stiffness and stage of graft fibrosis before antiviral therapy and on follow-up completion

Liver stiffness (kPa)	Stage of fibrosis	Number of patients before AVT, n (%)	Number of patients on follow-up completion, n (%)
less than 8.1	0	18 (54.5)	26 (78.8)
no less than 8.1	1	8 (24.2)	6 (18.2)
no less than 12.3	2	6 (18.2)	0
no less than 16.5	3	0	0
no less than 17.6	4	1 (3)	1 (3)

As can be seen from the Table, the severity of fibrosis upon follow-up completion decreased by 2 stages in 4 (12.1%) patients, by 1 stage in 8 (24.2%) patients. In 19 cases (57.6%), the stage of fibrosis did not change; and in 2 (6.1%) patients, it increased by 1.

The correlation analysis did not reveal any relationship between the ALT, GGTP activities and the LS parameters assessed either before the start of AVT or after the follow-up completion. Meanwhile, there was a statistically significant decrease in the activity of both enzymes when comparing the medians before AVT and after the follow-up completion. The ALT activity was 58.5 (36;148.5) IU/L at the time of the initial TE; 22 (15;34) IU/L after the follow-up completion (p=0.0002, statistically significant). The GGTP activity was 94 (46;265) IU/L at the initial TE; 31 (18;89) IU/L after the follow-up completion (p=0.01, statistically significant).

The mean BMI at baseline was 26.6 (95% CI [25.3–28]) kg/m^2 with only 5 recipients having BMI greater than 30 kg/m^2 (maximum 34 kg/m^2). At the end of the follow-up period, BMI was 27.9 (95% CI [26.7–29.2]) kg/m^2; BMI values greater than 30 kg/m^2 (maximum 37.8 kg/m^2) were noted in 10 recipients. No statistically significant correlation was found between BMI and LS parameters for both study time points.

Discussion

We have shown that effective antiviral therapy for recurrent hepatitis C in liver recipients leads to a persistent and prolonged reduction in LS, which primarily suggests the reverse (or slow-down) of graft fibrosis development.

Transient fibroelastography is relatively easy to use, quickly gives results, but it has a number of limitations. High LS values can be caused by a number of various factors rather than by only fibrosis. The presence of active inflammation in the liver can affect the results of TE regardless of the fibrosis stage. U. Arena et al. (2008) showed that among patients having similar fibrosis stage assessed histologically, LS values were higher in the patients having necroinflammatory activity compared to those without it [8]. C. Rigamonti et al. (2008) identified three factors independently influencing TE results in liver transplant recipients with recurrent hepatitis C, namely: the stage of fibrosis ($p<0.0001$), the inflammatory activity grade ($p=0.0001$), and GGTP activity above 200 IU/L ($p=0.004$). Having demonstrated that TE results changed in parallel with grading ($r=0.63$) and staging ($r=0.71$), the authors made the conclusion that TE accurately predicts fibrosis progression in LT patients with recurrent hepatitis C [9]. On the contrary, in several studies conducted in immunocompetent patients, no relationship was found between histological signs of liver (necrosis and inflammation) and TE values in patients with liver disease of various etiologies [6, 10–12]. In our study, liver biopsy was not performed. To assess the severity of inflammation, we used the ALT activity values. However, we did not find a correlation between the ALT activity and LS any of the two time-points of measurements.

The presence of cholestasis also influences the LS values. In one study of 15 patients, successful billiary drainage for a billiary obstruction

in the absence of liver disease resulted in a LS decrease by 8.1 kPa [13]. High LS values may be associated with sinusoidal congestion due to heart failure [14, 15] or the investigation being performed shortly after a meal [16]. There are also specific limitations to the use of TE in liver recipients. This is associated with a slightly altered location of the graft in the subdiaphragmatic space, its slight dislocation three-dimensional move and the lack of the graft support by the native ligamentous structures of the liver. The results of TE performed in the first year after LT in the recipients of a liver fragment from a living related donor may be affected by accelerated graft regeneration [17]. In our group of patients, only 2 recipients received a liver lobe from a living related donor, in both cases the first TE was performed more than 12 months after LT.

Obesity and associated liver steatosis do not affect the results of LS measurement, but complicate the TE implementation. A special XL probe was developed for obese people. Authors from Croatia recently published the results of fibrosis assessment by TE in 175 liver transplant recipients, of whom a significant proportion had obesity (34%), diabetes mellitus (38%), graft steatosis (69%), and 47% had severe liver steatosis. In multivariate analysis, the GGTP activity was the only factor significantly and independently associated with progressive fibrosis [18]. We failed to identify a relationship between GGTP activity and LS measured either before AVT or on completion of the follow-up period. We should note that our group of recipients had significantly lower BMI values and obesity rates compared to those discussed above. Thus, it is most likely that the change in LS in our recipient population primarily reflected the severity of graft fibrosis.

The effect of HCV eradication on the LS reduction and, accordingly, graft fibrosis could in reality have been more pronounced than we were able to demonstrate. First, it can be assumed that the long

period from the initial LS measurement to the start of AVT contributed to the fibrosis progression due to the retained viral replication, i.e., the initial LS values in this case were lower than at the start of AVT. Most of our recipients started AVT soon after the initial LS measurement (median 4.5 months); but in 9 cases, the period between the initial LS measurement and the start of AVT ranged from 14 to 34 months. On the contrary, a long follow-up period after the AVT completion could hypothetically have contributed to the launch of the non-viral mechanisms of graft fibrosis progression (steatohepatitis, autoimmunity, alloimmunity). In one of our patients, after successful treatment for recurrent hepatitis C, HBV reactivation (hepatitis B de novo) was noted, and HBV DNA in the blood remained at the level of 10^4 IU/mL throughout the follow-up period, despite the entecavir therapy. At the same time, no changes in LS were noted over 39 months of follow-up (5.6 kPa initially; 5.7 kPa at the end of follow-up). In another case, a recipient developed anastomotic stricture after successful HCV eradication, which required a series of surgical interventions on the biliary tract, culminating in a reconstructive operation. During a long-term follow-up period (92 months), the LS values did not change either (6.9 kPa initially; 7 kPa at the end of follow-up). Some of our patients had risk factors for steatohepatitis (diabetes mellitus, obesity, dyslipidemia, the return to significant alcohol consumption). It is possible that the impact of these and other non-viral factors over several years of follow-up leveled the effect of antiviral therapy for hepatitis C on LS and did not induce a decrease in the graft fibrosis stage in 19 of our recipients, in whom it remained the same. Interestingly, an increase in the fibrosis stage by 1 during the follow-up period was noted only in 2 recipients without obvious risk factors.

A number of prospective studies of patients with chronic liver diseases of various etiologies have shown that TE has a good diagnostic accuracy in detecting severe fibrosis. However, TE was less accurate for diagnosing moderate and mild liver fibrosis, with significant differences in cutoff values across studies and patient populations. The sensitivity for detecting stages 2, 3, and 4 fibrosis was 55–67%, 65–85%, and 76–87%, respectively, and the respective specificity was 84–90%, 85–95%, and 91–97 % [11, 19].

A number of studies have been published on the validation of TE results, based on histological examination of liver tissue performed in liver recipients with recurrent hepatitis C. Most investigators provided threshold values of liver stiffness to differentiate between consecutive stages of graft fibrosis, but in clinical practice it is considered correct to use TE to separate patients with severe (F2–F4) from those with mild (F0– F1) graft fibrosis. A. Carrion et al. (2006) set a cut- off point of 8.5 kPa for recipients with recurrent hepatitis C and stage 2 fibrosis. In this analysis, the area under the ROC curve was 0.9 [20]. N. Cholongitas et al. (2010) in a systematic review provided different LS cut-off values for severe fibrosis (stage 2 and higher; 7.9–10.1 kPa) and cirrhosis (10.5–26.5 kPa) in liver transplant recipients with recurrent hepatitis C (AUROC 0.89–0.94 and 0.87–0.98, respectively) [21]. A meta-analysis conducted by investigators from Canada (2017) included studies with different LS cut-off values for the fibrosis considered severe. The range of such values was from 7.3 kPa to 12.3 kPa [22].

We believe, one of the most methodologically correct studies, was the study by B. Della-Guardia et al. (2017) [7]. This study included the largest number of recipients among those published previously. Liver biopsy was performed in 267 patients (200 of whom had hepatitis C). TE was performed on the same day in 259 patients. When validating the TE

results, the investigators took into account the range of results obtained by different researchers or at repeated examinations by the same specialist. The authors established the following LS cut-off values in patients with recurrent hepatitis C: 8.1 kPa for fibrosis stage 1 and higher; 12.3 kPa for stage 2 and higher; 16.5 kPa for stage 3 and higher, and 17.6 kPa for fibrosis stage 4. Interestingly, those values were the highest among those previously reported in the literature for this patient population [20, 23-26]. To evaluate our results, we applied this classification with the most rigorous approach to fibrosis staging with respect to the TE results.

In early publications, repeated or serial studies of LS were aimed at predicting the outcome of recipients with recurrent hepatitis C amid its natural course. The efficacy of AVT with pegylated interferon and ribavirin in this patient population did not exceed 25%. Thus, in the study by C. Rigamonti et al. (2008) 90 liver transplant recipients, 89 of whom had recurrent hepatitis C, underwent liver biopsy and TE at least 6 months after LT and later on, up to 13 years after LT (median 35 months). In 40 cases, paired sequential studies were performed, with an interval of 6 months (21 patients), 12 months (16 patients), and 18–21 months (3 patients). The authors found that the area under the (AUC) of the TE results allows one to predict severe graft fibrosis with an accuracy of 0.85 and avoid performing a biopsy in patients with stable TE results during their follow-up [9].

In a prospective study, G. Crespo et al. (2014) showed that the cumulative probability of the liver function decompensation 5 years after LT was 8% in patients with LS less than 8.7 kPa one year after LT compared to 47% in patients with LS at least of 8.7 kPa ($p<0.001$, statistically significant). The 5-year overall graft and patient survival rates were 90% and 92% in patients with LS less than 8.7 kPa ($p<0.001$,

statistically significant) and 63% and 64% in patients with LS at least 8.7 kPa, respectively ($p<0.001$, statistically significant). Moreover, patients with low LS values one year after LT had good survival rates regardless of AVT and SVR. In contrast, graft survival was significantly improved only in those patients with LS of at least 8.7 kPa who achieved SVR [27].

With the implementation of new direct-acting antivirals (DAAs) into routine clinical practice, the assessment of the disease development prognosis in the natural course of recurrent hepatitis C lost its relevance. All recipients in whom HCV RNA is detected in blood at the time of LT are subject to AVT as early as possible. In immunocompetent patients with chronic hepatitis C, achieving SVR was associated with a TE-assessed improvement in liver stiffness [28]. In another study, significantly lower LS values were reported in a group of 47 patients with SVR compared to a group of 51 patients without SVR [29]. According to J. Chan et al. data (2018), LS regression of more than 30% from the baseline was observed by the 12th month after completion of DAA therapy in almost half of the patients [30]. There are also other reports confirming a TE-assessed LS decrease after AVT in patients with chronic hepatitis C. Unfortunately, there are few published reports on the assessment of the TE role for liver transplant recipients who complete effective AVT. Thus, E. Mauro et al. (2018) studied the effect of SVR achieved as a result of effective AVT on the fibrosis reversibility and the portal hypertension severity in liver recipients with recurrent hepatitis C. The authors examined 112 liver recipients who achieved SVR between 2001 and 2015. Liver biopsy was performed before AVT and 12 months after SVR had been achieved. At the same time, the hepatic vein pressure gradient (HVPG) and LS were assessed. Based on the histological examination of liver tissue, the regress of fibrosis was observed in 67% of recipients: in 43% of recipients with liver cirrhosis, in 72–85% at other

stages (p=0.002, statistically significant). These changes correlated well with the HVPG and LS parameters. Moreover, the reduction in graft fibrosis correlated with improved liver function and graft survival [31].

Conclusion

The value of our study lies in the length of patient follow-up. The median follow-up after the end of AVT was 54 months. Such a long follow-up period did not allow us to identify early changes in LS that occurred in the first 12 months after the end of AVT, but allowed us to talk about the stability of these changes over 4.5 years of follow-up. Thus, we have shown that an effective antiviral therapy leads to a stable decrease (over 4–5 years) in liver stiffness, which is largely due to the slowing down and reversal of liver fibrosis development.

On the basis of the study results we can make the following conclusions:

- After successful antiviral therapy, in most patients (57.6%), the stage of graft fibrosis did not change during a long-term follow-up (from 37 to 59 months). In 36.3% of cases, a decrease in fibrosis by 1–2 stages was seen. Only in 6.1% of cases, an increase in the fibrosis by 1 stage was observed.
- The impact of HCV-related risk factors on liver stiffness values in liver transplant recipients is insignificant.
- No statistically significant correlation was found between liver stiffness and blood levels of alanine aminotransferase and γ-glutamyl transpeptidase, body mass index, either before or after antiviral therapy. Meanwhile, a statistically significant decrease in the level of these enzymes was noted after successful treatment of hepatitis C ($p<0.005$).

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