Direct Acting Anti-Viral Therapy for Chronic Hepatitis C Virus Infection Is Associated with Regression of Liver Fibrosis, Assessed by Serial Transient Elastography (Fibroscan)

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Abstract

Background: Liver fibrosis stage determines risk of morbidity and mortality from chronic hepatitis C virus (HCV) infection. Prior data has shown long-term reversal of liver fibrosis, measured by transient elastography (Fibroscan), in patients successfully treated with interferon-based therapies. Our study sought to determine the effect of treatment with modern HCV direct acting anti-viral (DAA) therapy on non-invasive liver fibrosis measurements.

Results: A total of 78 patients had Fibroscan-based liver stiffness measurements (LSM) taken before treatment, directly after treatment completion, and at least 12 months after completion of DAA therapy. The sustained virologic response (SVR) rate in our cohort was 93.6%. Our outcome of interest was >30% decrease in Fibroscan score at 12 months post-treatment, relative to baseline. In our cohort 37 (47.4%) met the primary outcome. Those who had a baseline Fibroscan score of >7.3 kPa, signifying significant baseline fibrosis, had higher odds of meeting that outcome (OR 4.78; 95% CI 1.53-14.90), and this remained significant after controlling for baseline BMI, elevated ALT and elevated alkaline phosphatase levels.

Conclusion: Treatment of chronic HCV with modern DAA therapy was associated with a significant improvement in liver stiffness measurements by Fibroscan, suggesting improvement in liver fibrosis over the first year after treatment completion.

Introduction

- Liver fibrosis stage determines risk of morbidity and mortality from chronic HCV infection.
- Vibration controlled transient elastography (VCTE) using the Fibroscan (Echosens, France) platform is an accurate non-invasive measure of liver fibrosis in patients with chronic viral hepatitis.[1]
- Sustained virologic response (SVR) from interferon-based therapies was associated with regression of fibrosis over time.[2]
- Short-term follow-up (3-6 months post-treatment) has suggested improvement in fibrosis in response to treatment with DAA therapy.[3-4]
- Liver stiffness measured by Fibroscan post-SVR predicts risk of hepatocellular carcinoma[5] and other liver-related events.[6]
- We sought to assess the effect of HCV DAA therapy on changes in liver fibrosis, measured by transient elastography (Fibroscan), followed serially through 12 months after treatment completion.

Methods

- Study design: Prospective observational cohort.
- Transient elastography (Fibroscan) data: A valid Fibroscan consists of 10 valid acquisitions with the probe with a success rate of >60% and interquartile range of less than 30% of the median value. Study subjects were fasting for at least two hours prior to each Fibroscan.
- Fibroscan study time points: (1) pre-treatment, (2) end of treatment (EOT), and (3) 12 months post-treatment.

Methods (continued)

- Primary outcome: Significant improvement in liver fibrosis, defined as >30% decrease in Fibroscan score 12 months after end of treatment, relative to pre-treatment baseline.
- Data analysis: We performed univariate and multivariable logistic regression analysis to control for confounding.
- BMI, transaminitis, and elevated alkaline phosphatase levels were forced in to the multivariable model as fatty liver, liver inflammation, and cholestasis are known confounders of liver stiffness measurements.
- Signed rank test was used to assess change in liver stiffness measurement (LSM) between time points.
- All data analysis was performed on SAS.

Results

Table 1. Baseline characteristics (N=78)

Age in years (mean ± SD)	60.3 ± 9.7
Male (%)	52 (66.7)
Race (%)	
White	67 (85.9)
Black	7 (9.0)
Hispanic	3 (3.8)
Asian	1 (1.3)
BMI (kg/m^2) (mean ± SD)	27.1 ± 4.5
HCV Genotype (%)	
1	65 (83.3)
2	6 (7.7)
3	7 (9.0)
4	0 (0.0)
5	0 (0.0)
6	1 (1.3)
HCV viral load (IU/mL), median (IQR)	1,787,370 (1,035,000, 4,251,250)
HIV co-infected (%)	5 (6.4)
Diabetes (%)	10 (12.8)
Liver transplant recipient (%)	8 (10.3)
HCV treatment-experienced (%)	42 (53.8)
Severe fibrosis (Fibroscan score >7.3 kPa) (%)	48 (61.5)
Cirrhosis (Fibroscan score >13 kPa) (%)	21 (26.9)
Treatment regimen (%)	
Ledipasvir and sofosbuvir +/- ribavirin	42 (53.8)
Simeprevir and sofosbuvir +/- ribavirin	19 (24.4)
Sofosbuvir and ribavirin	10 (12.8)
PEG-interferon and sofosbuvir and ribavirin	4 (5.1)
Paritaprevir/r and ombitasvir and dasbuvir and ribavirin	3 (3.8)

Results (continued)

- Total enrollment: 127 HCV-infected patients
- Completed 12 month post-treatment Fibroscan (included in current analysis): 78
- SVR: 73 (93.6%)
- Relapse: 5 (6.4%)
- Primary outcome met (>30% improvement in Fibroscan score): 37 (47.4%)
- 1 of the 5 relapsers reached this outcome. That subject had evidence of liver inflammation and cholestasis, based on labs, which improved at the end of treatment.
- Of those with estimated baseline bridging fibrosis (Metavir stage ≥F3 or LSM >8.5 kPa), 17/44 (38.6%) improved to Metavir stage <F2 (LSM ≤7.3 kPa). Estimated Metavir stage cut-offs were based on data from paired liver biopsies and Fibroscans reviewed by Tapper EB et al.[7]
- Baseline LSM >7.3 kPa was associated with reaching the primary outcome, even after controlling for body mass index (BMI), and baseline elevated alanine aminotransferase (ALT) and alkaline phosphatase levels (OR=4.78; 95% CI 1.53-14.90) **(Table 2).**
- Significant improvement in LSM was also observed between the EOT and 12 month post-treatment time points, which suggests fibrosis improvement rather than LSM improvement solely due to resolution of inflammation associated with viral clearance **(Figure 1 and Table 3).**

Table 2. Univariate and multivariable analysis of baseline variables for association with achieving primary outcome (>30% improvement in Fibroscan score)

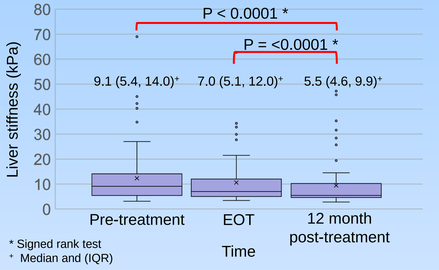
	Univariate		Mutivariable	
	Odds ratio (95% CI)	P *	Odds ratio (95% CI)	P *
Age (years)	1.03 (0.98-1.08)	0.30		
BMI (kg/m^2)	1.00 (0.91-1.11)	0.95	1.00 (0.89-1.12)	0.98
Male gender	0.42 (0.16-1.11)	0.08		
Genotype 1	6.42 (1.32-31.24)	0.02		
Elevated ALT	3.54 (1.39-9.07)	0.008	2.59 (0.93-7.24)	0.07
Elevated alkaline phosphatase	1.56 (0.52-4.72)	0.43	0.69 (0.19-2.44)	0.56
Prior HCV treatment experience	0.83 (0.34-2.02)	0.67		
Baseline Fibroscan >7.3 kPa	5.48 (1.96-15.31)	0.0008	4.78 (1.53-14.90)	0.007

* Continuous variables were analyzed using logistic regression. Categorical variables were analyzed using Fisher's exact test.

Note: When the multivariable model was run without "Baseline Fibroscan >7.3 kPa", the covariates "Genotype 1" and "Elevated ALT" were significantly associated with the outcome.

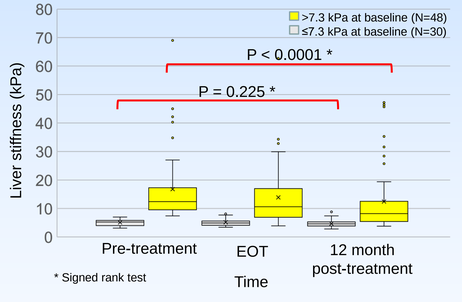
Results (continued)

Figure 1. Distribution of Fibroscan score over time (N=78)



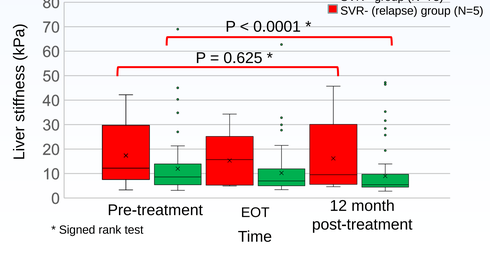
* Signed rank test
\+ Median and (IQR)

Figure 2. Distribution of Fibroscan score over time, stratified by baseline Fibroscan score



* Signed rank test

Figure 3. Distribution of Fibroscan score over time, stratified by SVR status



* Signed rank test

Results (continued)

Table 3. Median intra-patient changes in Fibroscan score during and after treatment

	All patients (N=78)		Baseline Fibroscan >7.3 kPa (N=48)	
Time point	Liver stiffness change (kPa), median (IQR)	P*	Liver stiffness change (kPa), median (IQR)	P*
12 months post-treatment vs. baseline	-2.9 (-4.9, -0.1)	<0.0001	-4.3 (-6.7, -1.9)	<0.0001
12 months post-treatment vs. EOT	-1.2 (-2.4, 0.0)	<0.0001	-1.6 (-4.0, -0.2)	0.0004
EOT vs. baseline	-1.6 (-3.7, 0.2)	0.0001	-2.5 (-6.3, -0.1)	<0.0001

* Signed rank test
NOTE: negative numbers correspond to improvement in Fibroscan score

Conclusions

- Treatment of chronic HCV with DAAs is associated with a reduction in liver fibrosis over the first year post-treatment (>30% decrease in Fibroscan score in 47.4% of subjects).
- Continued improvement in Fibroscan scores between EOT and 12 month post-treatment suggests regression of fibrosis rather than mere resolution of inflammation that occurs early after starting HCV therapy.
- Higher baseline Fibroscan score (>7.3kpa) was associated with achieving the primary outcome (>30% reduction in Fibroscan score).
- Among patients with high baseline fibrosis, the estimated Metavir fibrosis stage improved in approximately one third of patients.
- Longer term data is needed to determine whether improvement in liver fibrosis continues beyond one year, and larger studies are needed to elucidate factors associated with a more rapid or greater magnitude of improvement.

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