Regression of advanced fibrosis following virological suppression in response to anti-HCV therapy

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Disclosures

- MM, DHC and MD have nothing to disclose
- GJD is an advisory board member and has received honoraria from Roche, Merck, Janssen, Gilead, Bristol-Myers Squibb, Abbvie, has received research grant funding from Roche, Merck, Janssen, Gilead, Bristol-Myers Squibb, Vertex, Boeringher Ingelheim, Abbvie, and travel sponsorship from Roche, Merck, Janssen, Gilead, and Bristol-Myers Squibb.
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Background

- Assessment of hepatic fibrosis stage is crucial for prognosis and clinical management of chronic hepatitis C
- Liver-related complications occur in patients with advanced fibrosis, particularly cirrhosis
- Liver biopsy has been "gold standard"
  - Invasive procedure
  - Potential complications, cost, observer variability, sampling error, difficultly in performing repeated measures[1].
- Need for a non-invasive methods for disease staging

1. Rockey DC, Caldwell SH, Goodman ZD, Nelson RC, Smith AD. Hepatology. 2009;49:1017-44

Transient Elastography: FibroScan®

- Validated, non-invasive; rapid and reproducible
- Performs well in detection of cirrhosis
  - AUROC 0.90-0.98 with cut-off 11.9 kPa – 14.8 kPa
- Predicts long-term prognosis
  - Increasing LSM correlates with liver-related complications[2,3] and 5-year survival[4]
  - Marked increase in mortality with LSM >9.5kPa
- Improved histology with SVR; slows progression in relapse[5,6]
- Decrease in LSM and biomarker values with SVR[7,8]

2. Foucher J, Chanteloup E, Vergniol J, et al. Gut 2006;55:403-8; 3. Masuzaki R, Tateishi R, Yoshida H, et al. Hepatology. 2009;49:1954-61; 4. Vergniol J, Foucher J, Terrebonne E, Gastroenterology 2011;140:1970-9; 5. Poynard T, McHutchison J, Manns M, et al. Gastroenterology 2002;122:1303-13; 6. Carrima C, Di Bona D, Schepis F, et al. Hepatology. 2004;38:333-42; 7. Vergniol J, Foucher J, Castéra L, et al. J Viral Hepatitis. 2009;16:132-40; 8. Hézode C, Castéra L, Roudot-Thoraval F, et al. Aliment Pharmacol Ther. 2011;34:656-63

Aims

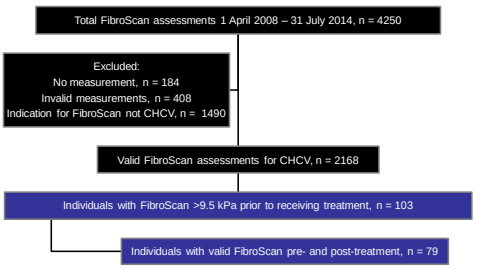
- ***Primary objective:***
  - To assess impact of chronic HCV treatment on LSM in those with severe fibrosis (F3, 9.6 – 12.5 kPa) or cirrhosis (F4, LSM >12.5kPa) as determined by LSM regression
    - Regression defined as reduction in LSM by >20% post treatment as compared with baseline
- ***Secondary objectives:***
  - To assess the impact of chronic HCV treatment on LSM in those with severe fibrosis or cirrhosis as determined by LSM regression to <F3 (<9.6 kPa)
  - To assess the impact of IFN-containing as compared with IFN-free treatment for chronic HCV
  - To determine variables associated with LSM regression

Methods

Retrospective (and prospective) cohort study

- **Cohort inclusion criteria**
  - ***Retrospective cohort***
    - Chronic HCV
    - FibroScan within 12 months of HCV treatment and LSM >9.5 kPa
    - Repeat FibroScan post-treatment
- **FibroScan inclusion criteria**
  - ≥10 valid measurements
  - Success rate >60%
  - IQR/median LSM <0.3 (if median kPa >7.0)

Methods

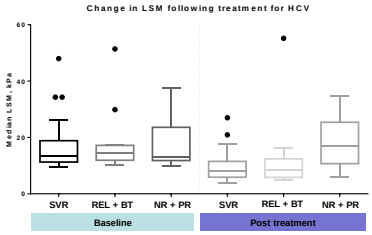


Results

Baseline Characteristics	All treated (n = 79)	SVR (n = 50)	Relapse and breakthrough (n = 14)	NR and PR (n = 15)
Age (years), mean	55	54	55	59
Male, n (%)	65 (82%)	46 (92%)	10 (71%)	9 (60%)
HIV, n (%)	14 (18%)	12 (24%)	2 (14%)	0
Baseline LSM, n (%)				
F3 (9.6 - 12.5 kPa)	32 (41%)	23 (46%)	4 (27%)	5 (36%)
F4 (>12.5 kPa)	47 (59%)	27 (54%)	11 (73%)	9 (64%)
HCV genotype, n (%)				
1	45 (58%)	28 (56%)	9 (64%)	8 (53%)
2	1 (1%)	1 (2%)	0	0
3	30 (38%)	20 (40%)	4 (29%)	6 (40%)
Other	3 (3%)	1 (2%)	1 (7%)	1 (7%)
HCV RNA (log_{10} IU/mL), median	5.9	5.9	6.6	5.8
ALT (U/L), median (IQR)	114 (69 - 157)	121 (68 – 157)	111 (76 – 151)	102 (64 – 184)

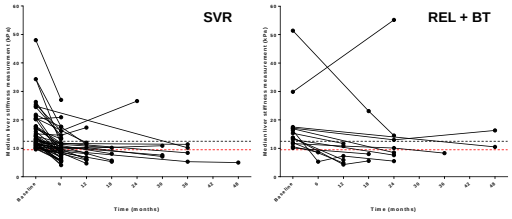
Results

Treatment variables	All (n = 79)	SVR (n=50)	Relapse and breakthrough (n=14)	NR and PR (n=15)
Treatment experienced, n (%)	18 (23%)	15 (30%)	2 (14%)	1 (7%)
Regimen, n (%)				
PEG-IFN + RBV	36 (46%)	17 (34%)	8 (57%)	11 (73%)
PEG-IFN + RBV + 1st gen PI	30 (38%)	22 (44%)	6 (43%)	2 (13%)
Other DAA regimen	13 (17%)	11 (22%)	1 (7%)	1 (7%)
IFN-containing, n (%)	71 (90%)	43 (86%)	14 (100%)	14 (93%)
Clinical trial, n (%)	27 (34%)	20 (40%)	5 (33%)	2 (13%)
Duration (weeks), median	26	29	29	13
Time intervals (weeks), median				
Baseline FS to treatment	10	16	5	7
EOT and post-treatment FS (1st)	27	25	26	56
EOT and post-treatment FS (Last)	40	31	52	120

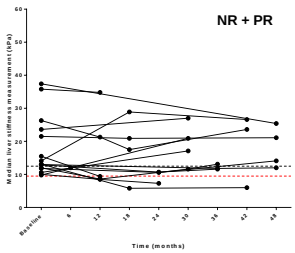


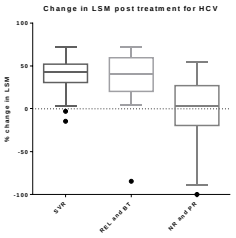
	SVR (n = 50)	REL and BT (n = 14)	NR and PR (n = 15)
Baseline LSM (kPa), median (IQR)	13.3 (11.4 – 18.3)	14.6 (12.3 – 16.9)	13.1 (11.9 – 22.6)
Post treatment LSM (kPa), median (IQR)	8.3 (5.9 – 11.4)	8.4 (6.3 – 11.4)	17.1 (11.4 - 24.5)
Change post treatment (kPa), median (IQR)	5.5 (4.0 – 8.2)	6.3 (2.4 – 8.1)	1.0 (-2.4 – 2.7)
P	<0.0001	0.0107	0.9231

Longitudinal LSM assessments



Longitudinal LSM assessments





	SVR (n = 50)	REL and BT (n = 14)	NR and PR (n = 15)
% change in LSM, median (IQR)	43% (31 – 52)	40% (22 - 59)	3% (-17 – 22)
Regression LSM >20% post treatment, n (%)	44 (88%)	11 (79%)	4 (27%)
Regression LSM <F3 post treatment, n (%)	30 (60%)	9 (64%)	3 (20%)

Factors associated with LSM regression >20%

Characteristic, n (%)	LSM regression >20% (n = 59)	OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
HIV co-infection					
Yes	13 (93%)	5.4 (0.8, 44)	0.12		
Treatment type					
PEG-IFN + RBV	23 (64%)	1.0	-		
PEG-IFN + RBV + 1st gen PI	24 (80%)	2.3	0.16		
Other DAA regimen	12 (92%)	6.8	0.08		
Treatment response					
SVR	44 (88%)	20.2 (4.8, 84)	<0.0001	20.2 (4.8, 84)	<0.0001
Relapse or breakthrough	11 (79%)	10.1 (1.8, 56)	0.008	10.1 (1.8, 56)	0.08
Null or partial	4 (27%)	1.0	-	1.0	-
Baseline LSM					
F3 (9.6 – 12.5 kPa)	25 (78%)	1.0	-		
F4 (>12.5 kPa)	34 (72%)	0.7 (0.3, 2.1)	0.56		

Factors associated with LSM regression <9.6

Characteristic, n (%)	LSM regression <F2 (n = 42)	OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
HIV co-infection					
Yes	10 (71%)	2.6 (0.7, 9.1)	0.14		
Treatment type					
PEG-IFN + RBV	16 (44%)	1.0	-		
PEG-IFN + RBV + 1st gen PI	19 (63%)	2.2 (0.8, 5.8)	0.13		
Other DAA regimen	7 (54%)	1.5 (0.4, 5.2)	0.56		
Treatment response					
SVR	30 (60%)	6.0 (1.5, 24.0)	0.011	6.9 (1.5, 32.8)	0.018
Relapse or breakthrough	9 (64%)	7.2 (1.4, 38.3)	0.021	12.3 (1.9, 81.3)	0.016
Null or partial	3 (20%)	1.0	-	1.0	-
Baseline LSM					
F3 (9.6 – 12.5 kPa)	25 (78%)	1.0	-	1.0	-
F4 (>12.5 kPa)	17 (36%)	0.16 (0.06, 0.44)	<0.0001	0.13 (0.04, 0.40)	<0.0001

Future directions

- ***Prospective cohort***
  - Inclusion criteria:
    - Chronic HCV
    - FibroScan LSM >9.5 kPa within 6 months of HCV treatment
  - LSM performed at:
    - Baseline
    - Post treatment - SVR 24, follow up year 1, year 2 (+/- year 5)
  - Additional data: BMI, abdominal circumference, alcohol use, diabetes control, lipid profile, liver-disease related complications
  - Additional objective: To determine incidence of liver-disease complications in those with F3/F4, including impact of LSM regression

Conclusions

- Virological suppression in response to HCV treatment results in LSM declines in patients with advanced fibrosis (F3/F4)
- The majority of patients with advanced fibrosis and SVR have significant liver disease regression, as measured by LSM
- Further data, particularly prospective cohort-based, is required to evaluate the impact of LSM declines on long-term prognosis
- Of particular clinical importance is whether ongoing HCC surveillance is required in patients with cirrhosis, who have LSM declines to <9.6 kPa