Influence of Markers Related to Biological Aging on Liver Regeneration in HCV Patients Achieving SVR

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BACKGROUND

- The achievement of sustained viral response (SVR) is associated with a reduction in liver stiffness (LS) in most patients and therefore, with a lower risk of suffering hepatic events.
- However, in a non-negligible percentage (10-30%) of patients who achieve SVR, LS is not reduced, and the responsible factors are not yet known.
- The analysis of markers related to cellular aging could offer an answer to this question.

METHODS

- A prospective study was conducted on parallel GEHEP and HEPAVIR cohorts at the Virgen de Valme University Hospital, which fulfilled the following criteria: 1) Achievement of SVR after 12 weeks of treatment with interferon-free direct-acting antivirals (DAA); 2) LS ≥ 9.5 kPa measured 3 months prior to DAA initiation; 3) Availability of LS measurement and sample on the SVR evaluation date.
- Telomere length (RTL) and levels of mitochondria, hsCRP, sCD163, sCD14, IL-6, Isoprostanate-8, CXCL10, CCL11, vWF, Vitamin D, and CHI3L1 were measured, and their association with the decrease or maintenance of LS at SVR was analyzed.

Characteristics of the population (n=175)

Variable	LS decrease (n=144)	No LS decrease (n=31)	p-value
Male sex, n (%)	118 (81.9)	29 (93.5)	0.110
Age (years)[1], n (%)	51.6 (48.3-54.4)	50.1 (41.2-57.3)	0.731
PWID, n (%)	106 (73.6)	22 (71)	0.763
Alcohol <50 gr/day[2], n (%)	31 (100)	134 (95)	0.205
Co-infection VHC/VIH, n (%)	81 (56.3)	17 (54.8)	0.886
CPT class A, n (%)	137 (95.8)	29 (93.5)	0.587
MELD index ≥10, n (%)	19 (13.4)	5 (16.1)	0.688
LS[1] pre-DAA (KPa)	16.8 (11.9-28.6)	14.4 (10.3-27.7)	0.287
LS[1] SVR (KPa)	11.7 (7.6-18.4)	21.3 (14.4-46.4)	<0.001
LS[1] change (KPa)	-5.3 [-10.1-(-2.7)]	4.2 (1.8-9.3)	<0.001

[1]Median (Q1, Q3); PWID, people with current or past injecting drug use; [2]In the last 6 months

Telomere length is independently associated with the absence of **liver regeneration** in people achieving **sustained viral response** to HCV

RESULTS

- A total of 175 patients were enrolled in the study. Among these, 31 patients (18%) did not experience a reduction in LS, with the LS values transitioning from a median (interquartile range, IQR) of 14.4 (10.3-27.7) kPa at baseline to 21.3 (14.4-46.4) kPa at SVR.
- Conversely, 144 patients (82%) demonstrated a significant decrease in LS at SVR.
- Univariate analysis revealed that telomere length, high-sensitivity C-reactive protein, and soluble CD163 exhibited an association with the absence of LS reduction at SVR.
- Variables such as HIV coinfection, baseline LS values, parenteral infection, HCV genotype 3, HCV viral load, as well as the Model for End-Stage Liver Disease (MELD) and Child-Pugh A scores showed no significant associations.
- In the multivariate analysis, adjusted for sex, age, hsCRP, and sCD163 levels, greater RTL emerged as the sole variable independently associated with the lack of LS reduction.

CONCLUSIONS

- Telomere length is independently associated with the absence of LS decrease in SVR.
- Greater cellular aging could be responsible, at least partially, for the absence of LS decrease in patients who achieve SVR.

Variables associated with absence of decrease in LS (n=175)

	Variable	LS decrease (n=144)	No LS decrease (n=31)	p-value
Senescence	RTL[1] (kb)	8.06 (5.7-11.2)	6.59 (5-8.4)	**0.011**
	mtDNA-CN[1]	141 (84-232))	159 (139-242)	0.217
Inflammation	hsPCR[1] (mg/l)	0.8 (0.35-1.91)	1.55 (0.63-4.25)	**0.008**
	IL-6[1] (pg/ml)	1.63 (0.7-2.6)	1.6 (0.7-5.3)	0.503
	CXCL10[1] (pg/ml)	96 (95-184)	96 (94-162)	0.229
	CCL11[1] (pg/ml)	418 (279-552)	475 (383-512)	0.295
	CHI3L1[1] (pg/ml)	813 (378-1283)	978 (342-1407)	0.287
Activation	sCD163[1] (ng/ml)	49.3 (39.8-58.4)	45.2 (38-47.9)	**0.045**
	sCD14[1] (ng/ml)	0.74 (0.61-0.99)	0.74 (0.58-0.95)	0.921
Hemostasis	vWF[1] (ng/ml)	26.8 (16.3-48.1)	27.7 (18.4-48.3)	0.771
Oxidative stress	Iso-8[1] (pg/ml)	140 (128-158)	133 (124-161)	0.530
Physiological funtions	Vitamin D[1] (ng/ml)	61.8 (48.7-72.9)	60.7 (42.8-70.8)	0.155

[1]Median (Q1, Q3); RTL, Relative telomere lenght; hsPCR, High sensitivity C-reactive protein; sCD163, soluble CD163; sCD14, soluble CD14; IL-6, Interleukin 6; CXCL10, Chemokine C-X-C Ligand with motif 10; vWF, von Willebrand Factor; Iso-8, Isoprostanate-8; CCL11, Chemokine C-C Ligand with motif 11; CHI3L1, Chitinase-3-like protein 1; mtDNA-CN, nº of copies of mitochondrial DNA.

Variables associated with absence of decrease in LS (n=175)

Variable	Adjusted odds ratio (95% CI)	p-value
Male sex	4.132 (0.473-36.12)	0.199
Age[1] (years)	0.981 (0.934-1.029)	0.426
RTL[1] (kb)	1.176 (1.021-1.354)	**0.025**
hsPCR[1] (mg/l)	0.988 (0.968-1.007)	0.207
sCD163[1] (ng/ml)	1.021 (0.984-1.058)	0.271

[1]Median (Q1, Q3); 95%CI: 95% confidence interval; RTL, Relative telomere lenght; hsPCR, High sensitivity C-reactive protein; sCD163, soluble CD163.

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