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Viral Kinetics Predict Response to All-Oral Therapy Against HCV Genotype 3 infection

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ABSTRACT

BACKGROUND/OBJECTIVES: Rates of sustained virologic response (SVR) to currently recommended therapy against hepatitis C virus (HCV) infection based on all-oral direct-acting antivirals (DAA) are generally high. However, in specific subsets, as it is the case for HCV genotype 3-infected, cirrhotic individuals, SVR rates can be suboptimal. The aim of this study was to determine the predictive capacity of response at week 4 for the achievement of sustained virologic response 12 weeks after the scheduled end of therapy date (SVR12) to treatment against HCV infection with all-oral DAA-based regimens.

METHODS: From a prospective multicohort study, patients who completed a course of currently recommended DAA-based therapy at 33 Spanish hospitals and who had reached SVR12 evaluation timepoint were selected. Treatment week 4 HCV-RNA levels were categorized in target not detected (TND), below the lower limit of quantitation (LLOQTD) and ≥LLOQ.

RESULTS: A total of 818 patients were included. SVR12 rates [n/N (%)] for HCV genotypes 1a, 1b, 3 and 4 in an on-treatment approach were 275/282 (97.5%), 283/286 (99%), 114/123 (92.7%) and 123/127 (94.5%). Of the HCV genotype 3-infected patients, 86 (70%) received sofosbuvir/daclatasvir+/-ribavirin, 27 (22%) sofosbuvir/ledipasvir/ribavirin and 10 (8.1%) sofosbuvir/ribavirin, respectively. In this subgroup, in those that achieved TND, LLOQTD and ≥LLOQ, SVR12 was 81 (97.6%), 24 (85.7%) and 9 (75%), respectively; p (linear association)=0.001. Corresponding numbers for HCV genotype 3-infected subjects with cirrhosis were: 52 (96.3%), 14 (77.8%) and 7 (70%); p=0.004. There was no association between response at week 4 and SVR12 for the other HCV genotypes.

CONCLUSIONS: Treatment week 4-response indicates the probability to achieve SVR12 to currently used DAA-based therapy in HCV genotype 3-infected individuals. This finding may be useful to tailor treatment strategy in this setting.

BACKGROUND

- The current standard-of-care for therapy against chronic hepatitis C virus (HCV) comprises almost exclusively an interferon (IFN)-free direct-acting antiviral (DAA) combination.
- Sustained virologic response (SVR) rates higher than 95% can be achieved with these new regimens.
- However, this is not true for all settings, such as specific patients with HCV genotype 3 infection.
- HCV genotype 3 is the second most common genotype in Europe and highly prevalent among injecting drug users in many low-income countries. There is furthermore evidence of this genotype being associated with a faster fibrosis progression, as well as the development of hepatic steatosis and hepatocarcinoma.
- Traditionally, on-treatment response played a role in the achievement of SVR and response-guided therapy (RGT) was applied both in the era of dual therapy with pegylated IFN plus ribavirin, as well as for the firstly approved DAA-based regimens.
- Whether there is an impact of viral kinetics on the SVR with DAA is some specific subsets remain unclear and data derived from clinical trials are controversial. Thus, an association between response during the first weeks of therapy was reported from the ALLY-3 trial, but could not be confirmed in the ALLY-3+ trial.
- This issue needs clarification, since it may help to develop strategies of RGT and thus optimize individual patient management.

OBJECTIVE

To determine the capacity of on-treatment response at week 4 of treatment to predict the achievement of SVR to therapy against chronic HCV infection with currently used, all-oral DAA-based regimens.

PATIENTS AND METHODS

- **Design:** Prospective multicohort study (HEPAVIR-DAA, clinicaltrials.gov ID: NCT02057003, GEHEP-MONO, clinicaltrials.gov ID: NCT02333292) in which all patients who consecutively attended 33 Infectious Diseases Units throughout Spain and who initiate therapy against chronic hepatitis C including any DAA-based regimen are included since October 2011.
- **Study population:** Individuals who fulfilled the following criteria were eligible for this analysis:
  - ✓ Initiation of IFN-free DAA-based therapy
  - ✓ Data on plasma HCV RNA available at treatment week 4
  - ✓ Having reached the SVR evaluation time point 12 weeks after scheduled end of therapy.

  Patients were not eligible for this analysis if they met one or more of the following exclusion criteria: i) Response could not be evaluated in an on-treatment approach, i.e. treatment was discontinued due to adverse events, patients were lost to follow-up or deceased; ii) HCV genotype 1 subtype was not or could not be determined or was other than 1a or 1b; iii) Infection with HCV genotype represented in less than 10 individuals or mixed infections; iv) Treatment regimen represented in less than 10 individuals.
- **Laboratory determinations:** HCV RNA levels in plasma were determined by PCR [Cobas AmpliPrep/Cobas TaqMan HCV test v2.0, Roche Diagnostic Corporation, Pleasanton, CA, USA, lower limit of quantitation (LLOQ): 15 IU/mL; Abbott M2000 Real Time System, Abbott Diagnostic, Chicago, IL, USA; LLOQ 12 IU/mL].
- **Classification of PCR results:** i) ≥LLOQ: HCV RNA quantifiable, reported as a specific IU/mL value, ii) <$LLOQ_{TD}$: HCV RNA levels below the LLOQ but detectable [target detected (TD)] and iii) target not detected (TND): undetectable HCV RNA.
- **Statistical analysis:** The outcome variable was SVR12, defined as undetectable HCV RNA 12 weeks after the scheduled end of therapy. The linear associations between the frequencies of SVR12 according and the response at treatment week 4 were assessed. For comparisons of 2x2 tables, the χ2 test or the Fisher's exact test were used. The positive predictive value (PPV), negative predictive value (NPV), specificity and sensibility, as well as the respective 95% confidence intervals (CI) of treatment week 4-response on relapse was determined. Statistical analysis was performed using the SPSS statistical software package release 23.0 (IBM, Chicago, IL, USA) and Fisterra.com (Elsevier 2012; http://www.fisterra.com/mbe/investiga/pruebas_diagnosticas/pruebas_diagnosticas.asp).

RESULTS

Table 1: Baseline characteristics of the study population according to HCV genotype.

Parameter	HCV genotype			
	1a (n=282)	1b (n=286)	3 (n=123)	4 (n=127)
Age (years)*	52 (47-55)	55 (50-66)	52 (47-55)	51 (47-54)
Male gender, no. (%)	219 (78)	179 (63)	91 (74)	101 (80)
Prior injection drug users, n (%)	125 (44)	62 (22)	64 (54)	65 (51)
Body-mass index (kg/m²)*	26 (22-29)	26 (23-29)	25 (21-27)	25 (23-29)
IL28B rs12979860 CT/TT, no. (%)§	128 (65)	137 (65)	39 (56)	59 (80)
HCV RNA >6*10⁶ IU/mL, no. (%)	44 (16)	38 (13)	17 (14)	19 (15)
HIV (+), no. (%)	124 (44)	53 (19)	64 (52)	67 (53)
Cirrhosis, no. (%)‡	144 (51)	144 (50)	82 (67)	63 (50)
CPT Index B/C, no. (%)#	22 (16)	18 (13)	9 (12)	7 (12)
Liver stiffness (kPa)*	12 (8.7-22)	12 (8.7-21)	16 (9.8-26)	11 (8.1-22)
Previous anti-HCV therapy, no. (%)§	139 (49)	160 (56)	77 (63)	69 (54)
DAA-experienced, no. (%)	10 (3.5)	14 (4.9)	5 (4.1)	1 (0.8)
Treatment regimens applied, no. (%)				
Sofosbuvir+simeprevir†	49 (17)	55 (19)	-	34 (27)
Sofosbuvir+daclatasvir†	9 (3.2)	14 (4.9)	86 (70)	-
Sofosbuvir+ledipasvir†	162 (57)	106 (37)	27 (22)	60 (47)
PTV/r+obitasvir+dasabuvir†	62 (22)	111 (39)	-	-
PTV/r+ombitasvir+ribavirin	-	-	-	33 (26)
Sofosbuvir+ribavirin	-	-	10 (8.1)	-
Use of ribavirin, no. (%)	133 (47)	103 (36)	64 (52)	66 (52)

CPT: Child-Pugh-Turcotte; DAA: direct-acting antivirals; ritonavir-boosted paritaprevir.
*Median (interquartile range); †available in 552 patients; ‡available in 412 patients with cirrhosis; #as determined by liver biopsy (F4 according to the Scheuer Index) or transient elastometry (12.5 kPa) if biopsy was not available; interferon-based therapy without DAA; §administered with or without ribavirin.

Of 1883 patients screened, 468 were excluded because they received IFN-based therapy, 3 patients received a regimen represented in <10 individuals, 12 patients, presented HCV genotypes represented in <10 individuals or mixed infections, 65 patients had an invalid HCV genotype 1 subtype determination, 138 had not reached SVR12 evaluation point, 13 patients were lost to follow-up, 11 patients voluntarily discontinued therapy, 3 patients discontinued due to adverse events and data on week 4 HCV RNA levels were missing in 352 subjects. Consequently, a total of 818 individuals were included in the analysis.

Figure 1: Treatment response according to HCV genotype (GT).

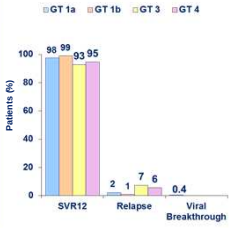

Figure 2: Rates of SVR12 according to response at week 4 of therapy.

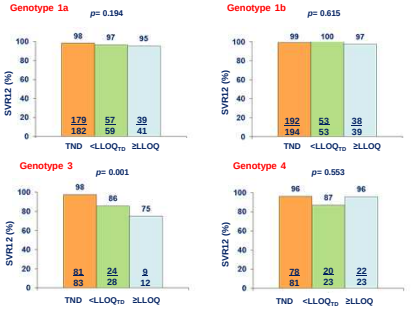

Figure 2: Rates of SVR12 among and according to response at week four of therapy in HCV genotype 3-infected patients with cirrhosis .
A: Overall cirrhotic population; B: HIV-coinfected patients; C: Subjects who concomitantly received ribavirin; D: Patients treated for 12 weeks; E: Subjects who received sofosbuvir+daclatasvir, with or without ribavirin; F: subjects who received sofosbuvir+ledipasvir+ribavirin.

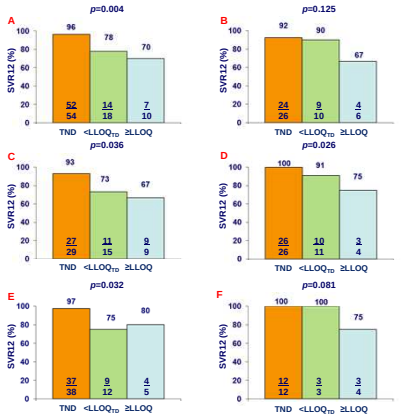

Table 2: Predictive values of response at treatment week 4 for relapse in HCV genotype 3-infected patients.

Predictive values	<LLOQ versus ≥LLOQ	TND versus TD
Overall population, n=123		
Sensitivity, % (95% CI)	33.3 (9-69.1)	77.8 (40.2-96.1)
Specificity, % (95% CI)	92.1 (85.1-96.1)	71.1 (61.7-79)
Positive predictive value, % (95% CI)	25 (6.7-57.2)	17.5 (7.9-33.4)
Negative predictive value, % (95% CI)	94.6 (88.1-97.8)	97.6 (90.8-99.6)
Misclassified patients, n (%)	15 (12.2)	35 (28.5)
Patients with baseline cirrhosis, n=82		
Sensitivity, % (95% CI)	33.3 (9-69.1)	77.8 (40.2-96.1)
Specificity, % (95% CI)	90 (80.1-95.7)	71.2 (59.3-81)
Positive predictive value, % (95% CI)	30 (8.1-64.6)	25 (11.4-45.2)
Negative predictive value, % (95% CI)	91.7 (82.1-96.6)	96.3 (86.2-99.4)
Misclassified patients, n (%)	13 (15.8)	23 (28.1)

CI: Confidence interval

CONCLUSIONS

- The on-treatment response indicates the probability of SVR to currently used DAA-based therapy in HCV genotype 3-infected individuals.
- This finding may be useful to develop RGT strategies in these patients, thus optimizing patient care to further close the gap in the response rates as compared to other genotypes.

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