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Analysis of variants associated with resistance of the new direct antiviral agents against HCV.

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Background

The use of novel direct antiviral agents (DAAs) against hepatitis C virus (HCV) has improved the results in response to treatment achieving sustained viral response (SRV) rates of up to 90%. The selection of resistance-associated amino-acid variants (RAVs) from HCV quasispecies, have been described as a possible cause of failure to antiviral DAA-combinations treatment; is dependent on drug-, host- and virus-related factors. The ability of a RAV to persist and to induce treatment failure (relapse, non-response or viral breakthrough) is related to its fitness or its replication capacity as compared to the wild-type virus.

Objectives

The aim of the study was to analyze the possible RAVs present in patients with failure to viral treatment.

Material/Methods

We selected all patients failing an all-oral DAA regimen (null-responder, breakthrough or relapsed) started between October 2014 and October 2016 in our hospital, (Complejo Hospitalario de Navarra, Pamplona; Spain).

Treatment failure was classified as

1.- Virological therapeutic failure (null-response, breakthrough or relapse).

2.- Non-virological therapeutic failure (adverse drug reaction, death and other causes non-related with treatment).

The HCV-RNA detection was performed during treatment (4th week of treatment and end of treatment) and 12 weeks after completion of treatment and/or thereafter.

Cobas® HCV (Roche Diagnostics, Mannheim, Germany) was used to perform HCV-RNA detection and genotyping with VERSANT® HCV Genotype 2.0 Assay (LiPA) (Siemens Healthcare Diagnostics, Tarrytown, NY, USA). RAVs´ sequential analysis was performed (nested-PCR and Sanger sequencing) at Spanish National Reference Laboratory (Majadahonda, Spain); NS5b region sequenced was partially sequenced. Mutant analysis was done according to Geno2pheno website.

Results

During the study period, 533 patients started an oral DAA regimen, and 23 (4,3%) failed therapy (figure 1). In 14 (61%) of them, the causes were related to treatment (7 relapsed, 4 null-responder and 3 breakthrough). HCV genotype distribution (failed therapy population) was 1a (43,5%),1b (26,1%), 3 (13%) and 4 (17,4%). 75% of patients were naive for antiviral therapy. Five samples from 4 different patients were studied to RAVs sequential analysis. The RAVs´ results are displayed in table 1. These analyses showed that all patients developed resistance to their received treatments. Patient nº1 and 2, developed resistance to NS5a inhibitors as ombitasbir, one of the drugs received. In patient nº3, the pre-treatment sample presented the C316Y RAV, associated with resistance to dasabuvir. Also post-treatment sample presented the C316Y RAV plus R30R and H58D both of them implicated in NS5a inhibitors´ resistance. All cases of genotype 1a studied presented the 444D RAV, a substitution at associated position.

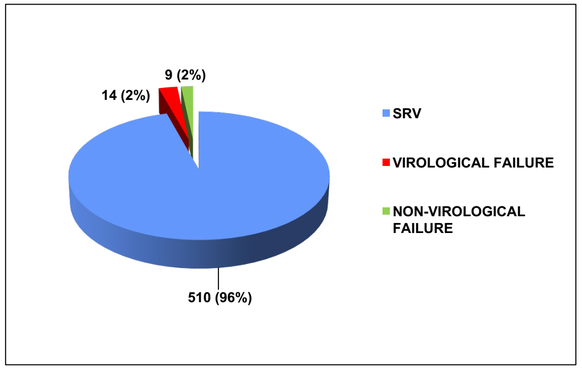

Figure 1. Strain distribution by treatment response.

Figure 2. HCV RNA sequence.

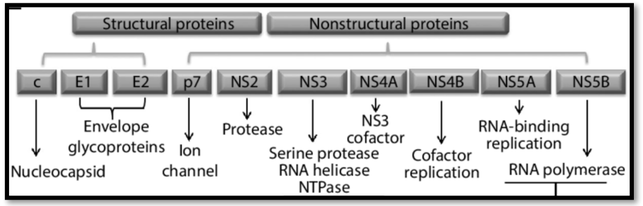

Table 1. RAVs sequential analysis results.

			Pre treatment			Post treatment		
	Genotype	DAA	NS3	NS5A	NS5B	NS3	NS5A	NS5B
Pac 1	1a	3D	na	na	na	174S	28T	444D
Pac 2	1a	3D	na	na	na	55A+80K	30R	444D
Pac 3	1a	3D	80L	-	316T+444D	-	30R+58D	316T+444D
Pac 4	1a	SOF+DCV	na	na	na	NL	93H	-

3D: ombitasvir, ritonavir, paritaprevir+dasabuvir; **SOF:** sofosbuvir; **DCV**: daclastavir

na= not available

NL=not licensed

Conclusions

- **In our study, all analysis demonstrated the presence of variants associated with resistance to treatments received by patients with treatment failure.**

Bibliography

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