THU-237

PREVALENCE AND CHARACTERIZATION OF NS5A RESISTANCE ASSOCIATED VARIANTS (RAVS) IN PATIENTS WHO RELAPSED FOLLOWING EXPOSURE TO NS5A INHIBITORS

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EASL The Home of Hepatology
THE INTERNATIONAL LIVER CONGRESS™ 2016
APRIL 13-17, BARCELONA, SPAIN

BACKGROUND

Recent data suggested that failure to achieve SVR with DAA therapy was usually due to relapse and is mostly associated with the emergence of resistance associated variants (RAVs).

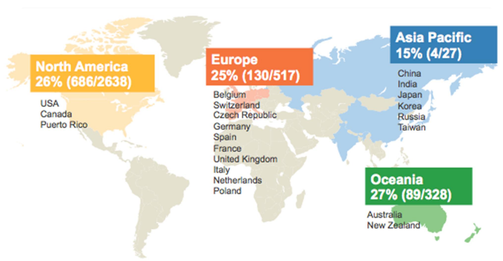
OBJECTIVES

The aim of this study was to investigate the prevalence and characterization of NS5A RAVs in 1500 patients infected with HCV genotype 1, 3 and 4 treated by DAA therapy including anti-NS5A in 4 French referent liver centers.

MATERIALS & METHODS

From January 2014 to September 2015, 1500 patients infected with HCV genotype 1, 3, and 4 were exposed to NS5A inhibitors (LDV/SOF, DCV/SOF, DCV/ASU) in the 4 French referent liver centers: Marseille, Lyon, Grenoble, St Laurent du Var. 22 (1.5%) of them relapsed: there were 18 males; fibrosis stage was F3 in three patients and F4 in 19 patients; HCV genotypes were G1a in 9 patients, G1b in six, G3a in six, and G4d in one; two patients were HIV-HCV coinfected, two were HBV-HCV co-infected, and 18 were HCV mono-infected. Prevalence of NS5A RAVs/polymorphisms was analyzed using Sanger sequencing. HCV subtypes and drug-resistance interpretation were identified using DeepChek-HCV software.

Figure 1.- Genotype 1a NS5a RAV Prevalence by Region (1% Cut-Off)



Using a 15% cut-off (akin to population sequencing), the prevalence of NS5A RAVs was 13% in North America, 14% in Europe, 7% in Asia Pacific, 16% in Oceania

G1a NS5a RAVs: K24G/N/R, K26E, M28A/G/T/V, Q30C/E/G/H/I/L/K/R/S/T/Y, L31I/F/M/V, P32L, S38F, H58D/L, A92K/T, Y93C/F/H/L/N/R/S/T/W

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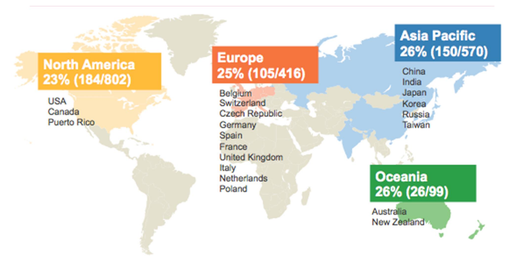
Figure 2.- Genotype 1b NS5a RAV Prevalence by Region (1% Cut-Off)



Using a 15% cut-off , the prevalence of NS5A RAVs was 16% in North America, 17% in Europe, 20% in Asia Pacific, 26% in Oceania

G1b RAVs: L28M, L31I/F/M/V, P32L, P58D, A92K, Y93C/H/N/S

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RESULTS

Numbers and characteristics of NS5A class RAVs (variants at any position associated with resistance to any NS5A inhibitors) from different genotypes are shown in table below. Main G1a RAVs detected were M28A, Q30H/K/R, L31M, H58D, Y93F/H/N; main G1b RAVs detected were L31F/M/V and Y93H; main G3a RAVs detected was Y93H; and main G4d RAVs detected was L28V. For only one G3a patient, no mutation was detectable at viral failure. Y93H was the most prevalent RAVs (55%) followed by L31M (23%). Ten out of 22 (45%) patients presented more than one RAVs which confers a higher level of resistance. No specific RAVs profiles based on the different NS5A inhibitors was found.

Table 1.- Resistance Associated Variants found in the 22 Relapsers

HCV Genotype	Number of Cases	Resistance Associated Variants																No Mutation
		K24Q	L28V	M28A	Q30R	Q30A	Q30K	Q30H	L31I	L31M	L31V	L31F	H54S	H58D	H58P	Y93H	Y93F	Y93N	
1a	9			1	1		3	1		1				1	1	1	1	1	
1b	6	1			2				1	2	2	1			2	6			
3a	6					2							2			5			1
4d	1		1																

Non-Resistant Variant | NS5A Resistance 10 - <100-fold | NS5A Resistance >100-fold | Major RAVs | Non-Reported RAV

CONCLUSIONS

- NS5A RAVs with high level of cross-resistance among NS5A inhibitors were found at the time of viral failure in more than 95% of patients whatever the genotype.
- These results strongly suggest that for patients who previously failed a regimen containing an NS5A inhibitor, NS5A RAVs screening is recommended when considering retreatment with a regimen containing an NS5A inhibitor.

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