High prevalence of NS3 resistance-associated substitutions in treatment naïve patients infected with genotype 1 of hepatitis C virus in Croatia

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BACKGROUND

It is estimated that between 35,000 and 45,000 of the Croatian population is chronically infected with HCV, with genotype 1 being the most widely distributed (57%) followed by genotype 3 (37%). Antiviral therapy for hepatitis C virus has been considerably improved with the introduction of direct-acting antivirals (DAA) that selectively target nonstructural proteins of the virus, among which is serine protease (NS3/4A). Resistance-associated substitutions (RAS) can be associated with inadequate treatment outcomes with DAA. The aim of this study was to analyze the frequency of substitutions associated with HCV resistance to NS3 inhibitors in treatment naive patients infected with HCV subtype 1a, 1b and 3a in Croatia.

METHODS

The study included 40 patients with chronic HCV genotype 1 and 18 patients with genotype 3 infection receiving clinical care at the Department of Viral Hepatitis of the University Hospital for Infectious Diseases, Zagreb between January 2019 and March 2020. HCV subtype was determined by using VERSANT HCV Genotype 2.0 Assay LiPA. Detection of substitutions associated with resistance to NS3 inhibitors was performed by population-based sequencing while resistance profile was analyzed in Geno2Pheno algorithm.

RESULTS

Resistance to NS3 inhibitors was detected in 13 of 40 (32.5%) of genotype 1 patients, 10 patients with subtype 1a (41.67%) and 3 patients with subtype 1b (18.75%). Additionally, 14 patients (35.0%) carried only mutations that cause reduced susceptibility to NS5A inhibitors, 7 patients in subtype 1a (29.17%) and 7 patients in subtype 1b (43.75%). Clade I of subtype 1a was detected in 18, and clade II in 6 patients with RAS present exclusively in clade I. All subtype 1a patients carried the same RAS, Q80K, associated with resistance to simeprevir. Resistance to NS3 inhibitors was detected in 1 of 18 (5.56%) of subtype 3a patients.

Table 1. Overview of resistance-associated amino acid substitutions, substitutions causing reduced susceptibility to NS3 inhibitors and uncharacterized substitutions in patients infected with HCV subtype 1a, 1b and 3a according to Geno2pheno algorithm (n/a: not applicable).

SUBSTITUTION	Subtype 1a	Subtype 1b	Subtype 3a
Resistance-associated substitutions			
54S	0	2	n/a
55A	0	1	n/a
80K	10	0	0
168R	0	n/a	1
Substitutions causing reduced susceptibility			
56F	0	6	n/a
117H	0	3	n/a
174S	10	n/a	n/a
Uncharacterized substitutions			
55I	0	2	0
80L	0	2	0
117C	0	1	0
117Y	0	1	0
122N	1	1	0
170I	0	8	0
170V	4	0	0
174A	0	1	0
174G	5	0	0
174L	0	1	0
174N	1	0	0

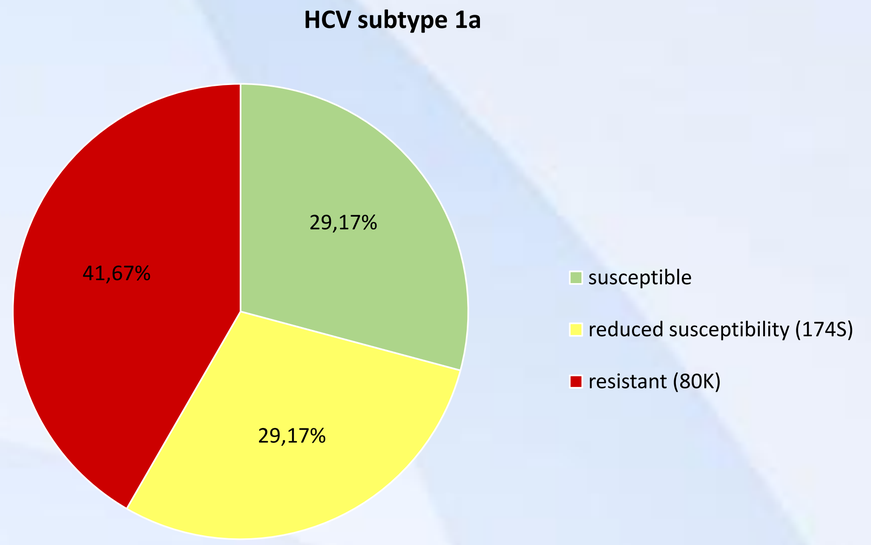

Figure 1. Amino acid substitutions associated with resistance in patients infected with HCV genotype 1a. 174S is a substitution associated with reduced susceptibility to telaprevir; 80K is clinically significant substitution associated with resistance to simeprevir; n=24.

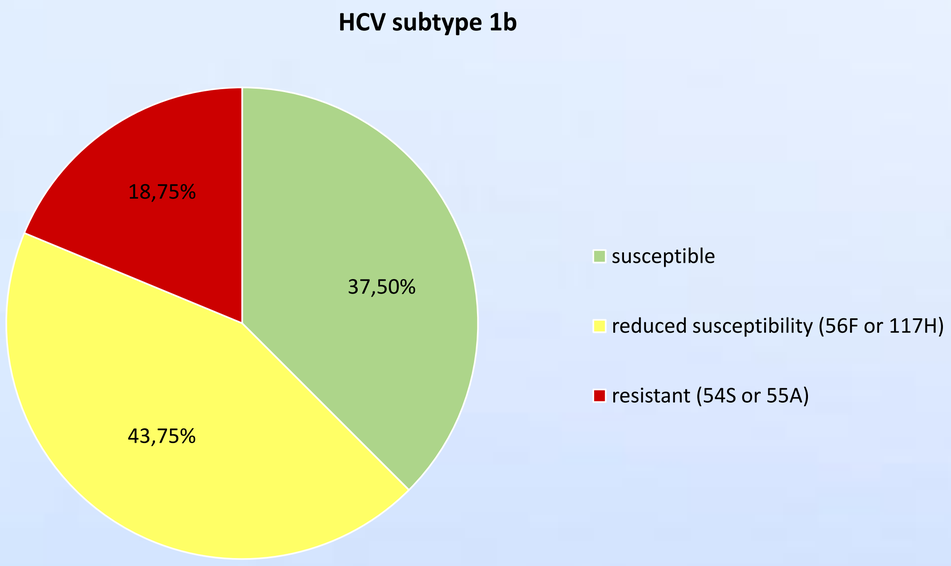

Figure 2. Amino acid substitutions associated with resistance in patients infected with HCV genotype 1b. 56F and 117H are substitution associated with reduced susceptibility to grazoprevir and telaprevir, respectively. 54S and 55A are clinically significant substitution associated with resistance to boceprevir; n=16.

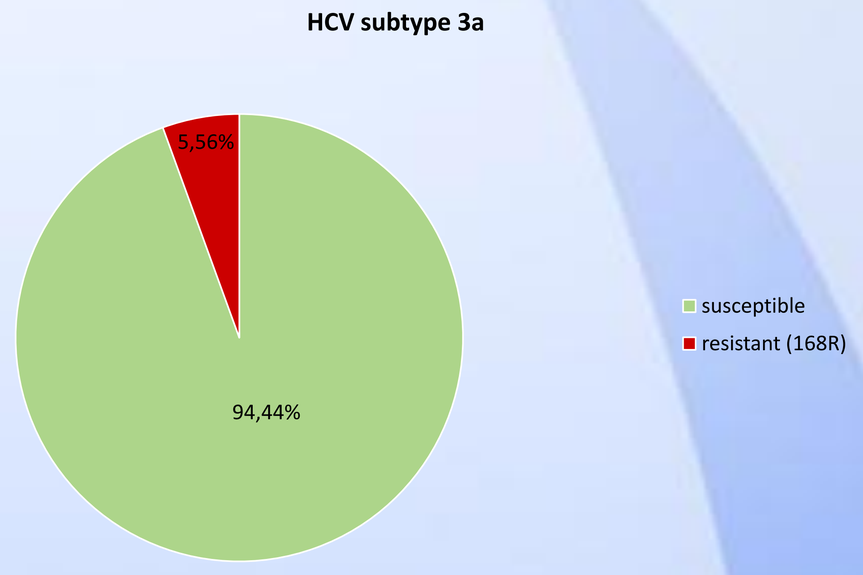

Figure 3. Amino acid substitutions associated with resistance in patients infected with HCV genotype 3a. 168R is clinically significant substitution associated with resistance to glecaprevir; n=18.

CONCLUSION

High prevalence of NS3 RAS was detected in patients infected with HCV genotype 1, especially subtype 1a. It is necessary to choose appropriate DAA combination in these patients in order to facilitate the achievement of sustained virological response.

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