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Predictors of treatment response in patients with hepatitis C 1b genotype

Research Article

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Abstract: Background: The aim of the study was to analyse the predictive host and viral factors of sustained virological response (SVR) in Estonian patients with chronic hepatitis C genotype 1b. Methods: A total of 76 outpatients (44 males and 32 females, aged 21-63 years) were enrolled in the single-centre prospective study. The patients received 180 μg of Peg-IFN α-2α weekly plus daily weight-based ribavirin (1000-1200 mg/day). Results: The SVR was achieved in 50% of the patients, 43.4% of the patients were referred to as non-SVR. The SVR and the non-SVR patients differed significantly in terms of age ($p=0.012$), stage of fibrosis ($p=0.012$), grade of inflammatory activity ($p=0.002$), platelet count ($p=0.005$), gamma-glutamyltransferase (GGT) level ($p=0.028$), as well as a decrease of the viral load at weeks 4 and 12 more than 3.59 log10 IU/ml and 5.98 $\log_{10}$ IU/ml ($P<0.01$), respectively. Conclusion: Age below 40 years, absence of or mild and moderate fibrosis, absence of severe inflammation activity, normal platelet count and normal GGT level, and pronounced changes in viral kinetics at weeks 4 and 12, were valuable predictors of better response to peginterferon alfa plus ribavirin treatment in Estonian patients with chronic hepatitis C genotype 1b.

Keywords: *Chronic hepatitis C • Genotype 1b • Pegylated interferon • Ribavirin • Sustained virologic response*

1. Introduction

Chronic hepatitis C (CHC) is a major cause of chronic hepatitis, cirrhosis and hepatocellular carcinoma worldwide [1]. The HCV has been classified into 6 major genotypes and a number of subtypes [2]. The HCV genotypes have a geographically distinct distribution [3]. Genotype 1b is the most prevalent in Southern and Eastern Europe, Northern America as well as in Japan [4].

In Estonia like in other East - European countries HCV subtypes 1b (71%) and 3a (24%) are prevalent [5,6]. Among Estonian patients hepatitis C virus has been reported as the main aetiological factor in about 75% of all chronic hepatitis cases [7].

A combination of pegylated interferon alpha (Peg-IFNα) and ribavirin (RBV) is the current standard of care for chronic hepatitis C [8,9]. The goal of antiviral therapy is eradication of HCV infection in order to prevent late complications of HCV-related liver disease and death [9].

The endpoint of CHC therapy is a sustained virological response (SVR), defined as HCV RNA negative at 6 months after completion of antiviral therapy [10].

However, SVR rates for patients infected with the most resistant HCV-1a and 1b genotypes are still unsatisfactory, ranging from 40 to 52% [11-14], so making this subset of HCV infected patients „difficult to cure" [15].

Bearing in mind the serious side effects of combination therapy, the possibility of its discontinuation and the

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cost, the prediction of treatment outcome is needed.

Various host and viral factors such as age, sex, race, stage of fibrosis, GGT level, body mass-index (BMI), HCV genotype, and viral load, as well as virus variability have been studied [16-24].

Rapid virological response (RVR), defined as an undetectable level of HCV RNA at week 4 and early virological response (EVR), with HCV RNA negative (complete EVR) or > 2 $\log_{10}$ drop (partial EVR) in HCV RNA at week 12, are the most reliable markers determining the duration and outcomes of Peg-IFN/RBV therapy for CHC patients with genotype 1 [25,26].

Several studies have recently identified individual polymorphisms near the human IL28B gene which is very significantly associated with SVR, particularly with genotype 1 [27].

Although a number of publications deals with prediction of treatment response, there is still a shortage of reliable predictive factors, especially for the „difficult to cure" subset of patients with 1b genotype.

This study aimed to analyse the predictive host and viral factors of SVR in Estonian patients with chronic hepatitis C genotype 1b.

2. Materials and methods

Seventy-six patients with chronic HCV-1b infection presenting to the outpatient clinic of West-Tallinn Central Hospital from February 2005 to March 2011 were enrolled in the study. Patient enrolment and their treatment were conducted according to the Estonian National Guidelines on treatment of CHC.

The diagnosis of CHC was based on the presence of HCV RNA in the sera, histologi¬cally verified fibrosis stage, degree of inflammatory activity and clinical follow-up. The treatment exclusion criteria were age <18 and >63 years, chronic alcohol intake, decompensated cirrhosis, current injection drug use and depression.

All patients were negative for antibodies to human immunodeficiency virus and to hepatitis B virus surface antigen.

Complete blood count, ALT, AST, GGT, bilirubin, TSH, and autoantibodies were measured at baseline and during treatment.

Serum HCV RNA levels at baseline and at weeks 4, 12, 24 and 48, and 24 weeks after treatment were analysed by the quantitative PCR assay (COBAS® AmpliPrep/COBAS® TaqMan HCV test, a lower limit of detection of 15 IU/mL, Roche, Branchburg).

The HCV genotypes were determined by the hybridization technique using a VERSANT HCV genotype assay (LiPA), Bayer Health-Care LLC, Tarrytown, NY.

Ultrasound-guided liver biopsy was performed on all patients. Stage of fibrosis was assessed by using Metavir score [28] as follows: F0 (no fibrosis), F1 (portal fibrosis without septa), F2 (portal fibrosis with rare septa), F3 (numerous septa without cirrhosis) and F4 (cirrhosis). Degree of inflammation was scored as A0 (no activity), A1 (minimal), A2 (moderate) and A3 (severe activity) [28].

All patients received 180 µg of Peg-IFN α-2α weekly plus daily ribavirin in a dose of 1000 or 1200 mg, depending on body weight (above or below 75 kg respectively). The patients were evaluated for achievement of RVR, EVR and SVR, and the impact of side effects on SVR was assessed.

Written informed consent for use of clinical data and serum samples was obtained from all patients prior to the study. The study was approved by the Tallinn Medical Research Ethics Committee.

2.1 Statistical analysis

Statistical analysis was performed as follows: the results were presented as mean ± SD. The χ^2 test, Fisher's exact test and Student's t-test were used. A *P* value of <0.05 was considered statistically significant. Univariate logistic regression analysis with calculations of odds ratios (OR), confidence intervals (CI) and P values was performed to explore the factors that could predict treatment outcomes.

3. Results

3.1 Baseline characteristics of the patients and treatment response

The demographic, laboratory and histological data of patients are summarized in Table 1. The current study included 44 males and 32 females with a mean age of 43±11.2 years. The male and female patients did not differ significantly in terms of age, BMI, fibrosis stage and inflammatory activity, platelet counts, or ALT level.

Although male patients showed a trend toward being younger and having higher ALT and higher viral load than female patients, the difference was not significant. Mean BMI was 26.7±4.9 kg/m^2. Normal BMI (≤25 kg/m^2) was recorded in 39.5% of patients and 60.5% (46/76) of the patients were overweight with a mean BMI of 29.8±2.03 kg/m^2.

Histologically, 82.9% (63/76) of the patients had fibrosis score F0 - 2 and 17.1% (13/76) of the patients had advanced fibrosis (F3-4). Among the latter cirrhosis was diagnosed in 9 patients. Of all patients, 40% had severe inflammatory activity (A3) irrespective of gender.

Table 1. Baseline characteristics of the study patients.

Characteristics	Male (n = 44)	Female (n = 32)	All patients (n = 76)	p- value
Age (years), range	21 – 58	21 – 63	21 – 63	
Mean ± SD	42.0 ± 10.9	44.1 ± 11.7	42.9±11.2	0.420
BMI (kg/m^2)				
Mean ± SD	26.5±3.9	26.9±6.11	26.7±4.9	0.704
≤ 25 kg/m^2, n (%)	16 (36.4)	14 (43.8)	30 (39.5)	0.635
> 25 kg/m^2, n (%)	28 (63.6)	18 (56.2)	46 (60.5)	
Viral load, n (%)				
≤ 0.6 mln IU/ml	8 (18.2)	9 (28.1)	17 (22.4)	0.405
> 0.6 mln IU/ml	36 (81.8)	23 (71.9)	59 (77.6)	
Mean ± SD-log$_1$0 IU/ml	6.13±0.41	5.98±0.55	6.07±0.47	0.179
Fibrosis stage, n (%)				
F 0 – 2	37 (84.1)	26 (81.3)	63 (82.9)	0.766
F 3 – 4	7 (15.9)	6 (18.7)	13 (17.1)	
Inflammation activity, n (%)				
0 –1	9 (20.5)	8 (25)	17 (22.4)	0.872
2	18 (40.1)	11 (34.4)	29 (38.2)	
3	17 (39.4)	13 (40.6)	30 (39.4)	
PLT, x 10^9 U/L				
Range	152 – 345	83 - 400	83 – 400	
Mean±SD	223.8±51.4	227.1±76.8	225.2±62.9	0.821
ALT, U/L, range	16 – 586	19 – 177	16 – 586	
≤ 42 U/L	5 (11.4)	8 (25)	13 (17.1)	0.136
> 42 U/L	39 (88.6)	24 (75)	63 (82.9)	
Mean ± SD, U/l	110.3±95.3	80.5±51.6	97.8±80.6	0.113
γ- glutamyltransferase, range	23 - 409	12 - 204	12 - 409	
≤ 61 U/L	19 (52.8)	21 (80.8)	40 (64.5)	0.032
> 61 U/L	17 (47.2)	5 (19.2)	22 (35.5)	
Mean ± SD, U/l	90.2±86.3	44.5±43.2	71.1±74.6	0.016

SVR, sustained virologic response; BMI, body mass index [kg/(height)^2], GGT, γ- glutamyltransferase (U/l)

Low platelet count (below 150 x 10^9 U/L) was reported in less than 8% (7/76) of the patients. Mean platelet count was 225.2±62.9 x 10^9 U/L without significant difference between male and female patients.

Elevated ALT level (>42 U/l) was determined in 82.9% (63/76) of the patients. Mean ALT level was 97.8±80.6 U/L at baseline.

Baseline GGT was available for 62 patients out of 76. The level of GGT in 40 (64.5%) of patients was in the normal range, being statistically higher in males than in females (90.2±86.3 U/L vs 44.5±43.2 U/L; p=0.016).
The mean baseline viral load was 6.07±0.47 log$_{10}$ IU/ml. The viral load was higher than 600 000 IU/ml in 77.6% (59/76) of the patients.

According to treatment response, 38 (50%) of all patients achieved SVR. Male patients had a higher SVR rate than female patients (57.9% vs 42.1%), although the difference did not reach significance (p =1.0).

Thirty-three (43.4%) of all patients did not achieve SVR and they were referred to as non-SVR. Of the non-SVR patients 18 (23.7%) were referred to as non-response (NR), i.e. patients in whom serum HCV RNA levels remained stable during treatment, and 15 (19.7%) were referred to as relapse (RL) patients, i.e. patients who sero-reverted to HCV RNA during follow-up. It is notable that all SVR patients and 8 of the 15 (53.3%) RL patients achieved complete EVR, while only 6 of the 18 (30%) NR patients and 7 (46.7%) of the RL patients achieved partial EVR.

The HCV RNA at week 4 was available for 42 patients, only 8 (19%) of them achieved RVR. Of the patients who achieved RVR, 6 were SVR patients and 2 were non-SVR patients.

Five of the 76 patients enrolled in the study stopped treatment due to side effects.

3.2 Comparison of the baseline characteristics of SVR and non-SVR patients

The SVR and the non-SVR patients differed significantly in terms of age, stage of fibrosis and grade of inflammatory activity in the liver, platelet count and GGT level.
The SVR patients were younger than the non-SVR patients (39.7 vs 46.1 years; p= 0.012), had less advanced stage of fibrosis F0-2 (94.7% vs 71.1%; p= 0.012), and less severe inflammatory activity A2 (55.3% vs 21.1%; p=0.002).

Only 2 patients of the 13 (15.4%) with severe fibrosis (F3-4) achieved SVR, while 11 did not.

Platelet count in the SVR patients was statistically higher compared to that in the non-SVR patients (245.1±61.4 x 10^9 U/L vs 205.3±58.5 x 10^9 U/L, p = 0.005).

The mean GGT level was 1.8 times lower in the SVR group than in the non-SVR group (50.4±45.0 U/l vs 91.7±91.6 U/l, p = 0.028). Among the patients with GGT level within the normal range, 25 (80.6%) achieved SVR, whereas among those with a high GGT level, only 6 (19.4%, p = 0.031) achieved SVR.

The other baseline characteristics such as gender, BMI, HCV RNA level, and ALT level were not significantly associated with SVR.

The baseline characteristics of the SVR patients as well as of the NR and RL patients were compared. The NR patients were significantly older (p=0.008), more overweight (p<0.05), had a more severe stage of fibrosis (F3-4) (p=0.031), and a higher degree of inflammation (p=0.0002), lower platelet count (p=0.031), and higher GGT levels (p<0.001) compared with the SVR patients.

There were no differences in the studied characteristics between the SVR and the RL patients.

High grade of inflammatory activity (p=0.038) and higher GGT levels (p=0.047) prevailed significantly in the NRs in comparison with the RLs.

3.3 Factors affecting SVR in univariate analysis

Univariate logistic regression analysis identified five baseline parameters that influenced significantly SVR: age below 40 years (OR 0.9521; CI 0.9108 - 0.9953, p = 0.0302), normal platelet count (OR1.0115; CI 1.0029 - 1.0201, p = 0.0084), normal GGT level (OR 0.9901; CI 0.9804 - 0.9999, p = 0.0469), absence of or mild and moderate stages of liver fibrosis (OR 0.6233, CI 0.4250 - 0.9143, p = 0.0156), and absence of or mild inflammatory activity (OR 0.5404, CI 0.3272 - 0.8925, p = 0.0162); correlation with BMI, pretreatment viral load and ALT level was not revealed.

However, the above parameters were not entered in multivariate analysis owing to the small number of studied patients, which made these parameters impossible to use as independent predictive factors in the current study.

3.4 Comparison of on-treatment factors and treatment response

Further, we analysed changes in on-treatment clinical features between the groups of patients (SVR vs NR, SVR vs RL, NR vs RL) at weeks 4 and 12 (Table 2).

Measurement of viral clearance from the serum revealed that only a more pronounced decrease of the viral load at weeks 4 and 12 distinguished significantly in the SVR patients (-3.59 and -5.98 $\log_{10}$ IU/ml, respectively) for both the non-responders and the relapsers ($p<0.01$). Similarly, the RLs showed a more significant decrease of the viral load compared to the NRs (- 4.89 $\log_{10}$ IU/ml and - 1.62 $\log_{10}$ IU/ml, respectively, $p<0.01$).

The other parameters such as ALT (p=0.002) and Hgb (p=0.05) levels, and leucocyte (p=0.02), and neutrophil (p=0.018) counts were significantly higher for the NR patients compared to the SVR and RL patients at week 12.

There were no differences in these parameters between the SVR, NR and RL patients at week 4.

3.5 Side effects of antiviral therapy

About 90% of the treated patients experienced several side effects of antiviral therapy. Besides blood abnormalities, there prevailed also fatigue, depression, myalgia and weight loss (>4 kg). Compared to patients with no response to therapy there were more persons among the patients with SVR who experienced depression, 36.8% (14/38) vs 13.2% (5/38), p = 0.033. This fact can probably be explained by extended treatment duration in SVR patients.

Five patients stopped treatment due to intolerance (fatigue, nausea) of therapy.

4. Discussion

Although significant improvements have been achieved in the treatment of patients with chronic hepatitis C, the current standard of antiviral therapy, consisting of pegylated IFN- α in combination with ribavirin, leads to SVR in only 42-52% of treatment-naïve patients with HCV genotype 1b infection [11-14].

Achievement of SVR is associated with a decrease in all-cause mortality, liver-related death and liver-related complications, as well as with the need for liver transplantation [29].

However, positive prediction of SVR is still difficult because of the different hosts and genetic and viral factors which have been described that are responsible for the variable HCV treatment outcome [16-23].

In the present study, we aimed to evaluate the efficacy of pegIFN-α plus ribavirin combination therapy in treatment-naïve patients with chronic HCV-1b infection, and to analyse the factors that might affect treatment response. For assessment of treatment efficacy we used SVR, RVR and EVR.

The rate of SVR in the current study was 50%, which is consistent with our previous data [30], as well as with the results obtained from clinical trials [12-15] and from "real life" clinical settings [31,32].

Moreover, previous studies have shown that younger age (< 40 years), normal GGT level, high ALT level, normal platelet count, absence of cirrhosis, low viral load, virus genotype and Caucasian race were more probably associated with better treatment outcomes [11-14,17,33]. Also, as suggested by Marcellin et al. [34], referring to the PROPHESYS database, a simple scoring system including such factors as age, BMI, viral load, platelet count, ALT level and ALT/AST ratio can help identify HCV-1b patients who can benefit from therapy with pegylated interferon and ribavirin.

According to our data, age below 40 years, normal platelet count, normal GGT level, absence of or mild and moderate stages of liver fibrosis, and absence of or mild inflammatory activity predicted SVR in the studied patients. However, patient gender, BMI, viral load and ALT levels were not associated with treatment outcomes. Absence of association of gender and BMI with treatment outcomes was also shown in several large prospective studies [11,12,24]. It is also worth noting, that although 61% of our patients were overweight (BMI > 25 kg/m^2) their mean BMI (29.8±2.03 kg/m^2) was not drastically high compared to that of patients with normal weight.

Absence of correlation between virological response, viral load and ALT level may be explained by the small number of patients enrolled in our study in comparison

Table 2. On-treatment clinical features of studied patients at weeks 4 and 12: SVR vs NR, SVR vs RL, NR vs RL.

	SVR vs NR			SVR vs RL			NR vs RL		
	SVR, n =38	NR, n = 18	p - value	SVR, n =38	RL, n = 15	p - value	NR, n = 18	RL, n = 15	p - value
ALT, U/L									
At week 4*									
Range	10-163	17-200		10-163	15-113		17-200	15-113	
Mean±SD	43.4±32.2	60.9±46.9		43.4±32.2	51.7±34.5		60.9±46.9	51.7±34.5	
≤ 42 U/L	23 (60,5)	7 (41.2)	0.124	23 (60.5)	7 (46.7)	0.441	7 (41.2)	7 (46.7)	0.537
> 42 U/L	15 (39.5)	10 (58.8)	0.245	15 (39.5)	8 (53.3)	0.539	10 (58.8)	8 (53.3)	1
At week 12									
Range	10-101	14-177		10-101	9-119		14-177	9-119	
Mean±SD	33.8±20.4	64.7±49.3		33.8±20.4	34.3±22.8		64.7±49.3	34.3±22.8	
≤ 42 U/L	30(70.9)	9 (50.0)	0.002	30(70.9)	11 (73.3)	0.946	9 (50.0)	11 (73.3)	0.044
> 42 U/L	8 (21.0)	9 (50.0)	0.035	8 (21.0)	4 (26.7)	0.722	9 (50.0)	4 (26.7)	0.284
Hgb									
At week 4*									
Range	84-166	106-160		84-166	101-149		106-160	101-149	
Mean±SD	129.3±17.6	133.7±16.9	0.386	129.3±17.6	128.3±3.9	0.848	133.7±16.9	128.3±3.9	0.332
At week 12									
Range	80-155	105-149		80-155	98-145		105-149	98-145	
Mean±SD	120.1±17.3	129.2±12.1	0.050	120.1±17.3	120.7±13.0	0.904	129.2±12.1	120.7±13.0	0.062
Leucocytes									
At week 4*									
Range	1.6-5.6	2.2-2.5		1.6-5.6	1.8-5		2.2-2.5	1.8-5	
Mean±SD	3.68±1.10	3.82±1.27	0.676	3.68±1.10	3.35±1.07	0.330	3.82±1.27	3.35±1.07	0.270
At week 12									
Range	1.6-5.7	1.9-7.6		1.6-5.7	1.5-5.2		1.9-7.6	1.5-5.2	
Mean±SD	3.04±0.93	3.82±1.47	0.020	3.04±0.93	2.94±1.04	0.735	3.82±1.47	2.94±1.04	0.062
Neutrophils									
At week 4*									
Range	0.8-3.1	0.9-3.7		0.8-3.1	0.6-2.6		0.9-3.7	0.6-2.6	
Mean±SD	1.67±0.65	1.88±0.86	0.334	1.67±0.65	1.39±0.57	0.155	1.88±0.86	1.39±0.57	0.075
At week 12									
Range	0.6-2.9	0.8-4.6		0.6-2.9	0.6-3.0		0.8-4.6	0.6-3.0	
Mean±SD	1.44±0.56	1.96±1.04	0.018	1.44±0.56	1.51±0.82	0.708	1.96±1.04	1.51±0.82	0.187
PLT									
At week 4*									
Range	71-368	63-319		71-368	100-247		63-319	100-247	
Mean±SD	177.8±63.5	161.2±72.6	0.396	177.8±63.5	163.6±38.8	0.155	161.2±72.6	163.6±38.8	0.909
At week 12									
Range	63-404	56-327		63-404	83-300		56-327	83-300	
Mean±SD	168.3±66.0	152.2±70.8	0.410	168.3±66.0	148.5±59.1	0.316	152.2±70.8	148.5±59.1	0.871
Viral load, Decrease from 0 wk to 4 wk - $\log_{10}$	- 3.59	- 1.24	<0.01	- 3.59	- 3.15	>0.05	- 1.24	- 3.15	<0.01
Decrease from 4wk to 12 wk - $\log_{10}$	- 2.39	- 0.38	<0.01	- 2.39	- 1.74	>0.05	- 0.38	- 1.74	<0.05
Decrease from 0wk to 12 wk- $\log_{10}$	-5.98	- 1.62	<0.01	-5.98	- 4.89	<0.05	- 1.62	- 4.89	<0.01

**In 1 NR patient blood tests were not taken at week 4*
Laboratory reference ranges: Hemoglobin (Hgb) - 110 – 150 g/l; leucocytes - 3.8-10.0x10⁹ U/l; neutrophils - 1.9-8.0x10⁹ U/L; platelets (PLT) -150-400x109 U/L, viral load – decrease log 10 IU/ml

with other studies [17,33], which rendered differences statistically non-significant. Therefore, we agree with Navaneethan et al. [35] in that the use of the above pre-treatment factors cannot accurately predict SVR in all patients.

Of the on-treatment factors, viral kinetics at weeks 4 and 12 can more precisely assess treatment outcomes. In case patients achieved RVR, the probability of attaining SVR would be 88 - 100% irrespective of genotype [26]. Also, the SVR rates of patients with genotype 1, who achieved complete EVR, varied from 68% to 84%, and the SVR rate of patients with partial EVR was reported to be 17- 29% [36].

Seventy-five percent of our patients with RVR achieved SVR and around 83% of those with complete

EVR attained SVR. Partial EVR was recorded in 13 (17%) of the patients who failed to achieve SVR, of those 6 were non-responders and 7 were relapsers. Bearing in mind this fact retrospectively, we can speculate that RLs could be benefit from the prolongation of antiviral treatment up to 72 weeks, however, in this study they were treated for 48 weeks as usual.

Viral kinetics in the studied patients revealed a more pronounced decrease of the viral load in those with SVR compared to those with no response to antiviral therapy ($p < 0.01$), with a tendency to a pronounced decrease of the viral load during the first 4 weeks of treatment in particular. Slight and slow decrease in the viral load in NRs could be explained by the appearance of resistance to antiviral drugs. Hence viral kinetics at weeks 4 and 12 could be a reliable predictor of treatment outcomes.
Combined therapy with pegIFN-α plus RBV can lead to changes in haematologic parameters [11-14], which can be considered a marker of pharmacodynamic effects. Lack of a haematologic abnormalities may indicate poor response to therapy [35].

The current study demonstrated that patients with marked haematological abnormalities achieved SVR better than patients with a smaller reduction in haematologic parameters.

In order to identify patients who could benefit from combined antiviral therapy and patients who could not, we performed a more detailed analysis of the host and viral characteristics at baseline and during treatment for different studied groups: SVR vs NRs, SVR vs RLs, NRs vs RLs. It appeared that almost all studied parameters differed significantly for NR and for SVR patients. The clinical pre- and on-treatment characteristics of the RLs were practically similar to those of the SVR patients, making the relapse patients very difficult to distinguish and to cure.

The present study has several limitations. First, it was a single - centre prospective study with a small cohort of study subjects, which could reflect the experience of only one out of five clinical centres providing treatment of CHC in Estonia. Second, we did not study polymorphisms of the human IL28B gene.

Of the viral factors, lack of diversity in genetic sequences, especially absence of amino acid mutations in the HCV NS5A gene, is a predictor of non-response to therapy for genotype 1b [38].

We performed the study to investigate the correlation between mutations in the entire NS5A protein and the treatment response in Estonian patients with chronic HCV-1b infection who received combined antiviral therapy. The results will be published soon.

In conclusion, the rate of treatment response in the studied CHC 1b genotype patients is generally similar with the corresponding rate reported in studies evaluating the efficacy of combination therapy of peg-IFN and RBV in treatment-naïve HCV genotype 1b patients. Statistical analysis showed that host factors, such as age below 40 years, absence of or mild and moderate fibrosis, absence of severe inflammatory activity, normal platelet count, normal GGT level, and viral factors, such as pronounced changes in viral kinetics at weeks 4 and 12 were valuable predictors of better treatment response.

At the same time, it is absolutely obvious that deeper insights into the nature of the virus are needed. Specifically, the genetic variability of the virus genome should be determined and used together with other host and viral factors as a predictive tool in clinical practice to treat the „difficult to cure“ subset of genotype 1b HCV patients. This would help lower costs of antiviral treatment and select patients who can benefit from dual or triple treatment.

Conflict of interest

The authors declare that they have no competing interests.

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