PREDICTORS OF SUSTAINED VIROLOGICAL RESPONSE (SVR) TO PEGYLATED INTERFERON ALPHA (PEG-IFN α) AND RIBAVIRIN (RBV) IN PATIENTS WITH CHRONIC HEPATITIS C INFECTED WITH GENOTYPE 1

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ABSTRACT

Objective: The combined PEG-IFN alpha and RBV therapy achieved SVR in 40 - 50% of patients infected with HCV genotype 1. Identification of virological and host paramemeters predicting SVR will be useful to tailor therapy.

Methods: 71 patients with chronic HCV genotype 1 infection were treated with PEG-IFN alpha2a and RBV for 12 months. Predictors of SVR were analyzed by using nonparametric correlation test.

Results: SVR was found in 57 / 71 of subjects (80,3%). The significant differences in baseline level of HCV RNA, sex, age, baseline ALT and present of liver cirrhosis between the patients with or without SVR were not found. Correlation was not proved between SVR and all these factors when they were analyzed separately. High correlation was found between serum levels of HCV RNA at the end of 3-th month therapy (Early Virological Response) and SVR (r=0,759; p=0,011).

Conclusion: The viral response during the first 3 months of PEG-IFN alpha and RBV therapy is the strongest independent predictor among the all baseline viral and host predictive factors for achieving of SVR.

Key words: HCV, HCV genotype 1, PEG-IFN, Ribavirin, predictors.

INTRODUCTION

Hepatitis C virus (HCV) infection is one of the main causes of chronic liver disease worldwide (1). It is estimated that approximately 130-210 million individuals are chronically infected with HCV (2). Chronic infection is associated with variable degrees of hepatic inflammation and fibrosis progression, regardless of HCV genotype and viral load. Depending on the presence of co-factors (alcohol consumption, diabetes mellitus, older age, HIV and HBV coinfections) between 10% and 40% of patients with chronic HCV infection will develop cirrhosis (3). Death related to the complications of cirrhosis is approximately 4% per year, whereas HCC occurs in this population at an estimated incidence of 1-5% pre year (4).

The combination of pegylated interferon alpha (PEG-IFN α) and Ribavirin (RBV) is the approved and well accepted standard–of-care (SoC) for chronic hepatitis C (5, 6, 7). The primary goal of HCV therapy is to cure the infection, which results in eliminating detectable circulating HCV after cessation of treatment. Sustained virological response (SVR) is defined as an undetectable HCV RNA level (<50 IU/ml) 24 weeks after treatment withdrawal. In patients infected with HCV genotype 1,SVR rates after SoC are on the order of 40% in North America and 50% In Western Europe in most trials. The SVR rates are considerably higher in patients infected with HCV genotypes 2 and 3 (65-82%).

Many predictors of SVR in patients infected with HCV genotype 1 were analyzed (8). Identification of favorable predicting factors is of clinical importance.

MATERIALS AND METHODS
Studied patients

We studied 71 patients with chronic HCV genotype 1 infection treated with SoC (PEG-IFN α2a 180 µg once per week s.c. and RBV 1 000 – 1 200 mg daily dose p.o.) for 48 weeks according National Health Insurance Program (tab. 1). All subjects initially were with active viral replication defined as detectable HCV RNA and histology proved liver disease. Co-infections with HBV, HDV and HIV were excluded.

Table 1. Baseline patients' characteristics

Number of patients		71
Gender	Male	35
	female	36
Age [years]	Median	31
	(min. – max.)	(18 - 63)
HCV RNA [IU/ml]	Median	586 118
	(min. – max.)	(3 422 - 27 400 000)
ALT [U/l]	Median	47
	(min. – max.)	(10 - 99)
Liver cirrhosis	YesNo	962

Treatment response

Sustained virological response (SVR) was defined as an undetectable HCV RNA level 24 weeks after treatment withdrawal analyzed by sensitive PCR (COBAS AMPLICOR or "real time" PCR).

Early virological response (EVR) was defined as HCV RNA undetectable at 12 week, maintained up to end of therapy (9).

Statistics

Predictors of SVR were analyzed by nonparametric methods and correlations.

RESULTS

SVR was achieved in 57 / 71 of subjects (80,3%). The rest 14 / 71 of patients (19,7%) did not achieved SVR.

The two groups of patients with or without SVR were compared each others by sex, age, ALT, baseline HCV RNA and present of liver cirrhosis (tab. 2)

Table 2. Baseline characteristics of patients with or without SVR.

Parameters (Median)	Sex (m/f)	Age (years)	ALT (U/l)	HCV RNA (IU/ml)	Cirrhosis (Y/N)
Patients with SVR	29 / 28	29,0	47,0	660 000	6 / 57
Patients did not achieved SVR	6 / 8	37,0	47,0	475 351	3 / 14

Between the patients with or without SVR did not found differences in sex, age, ALT, baseline HCV RNA and present of liver cirrhosis (tab. 3).

Table 3. The differences between patients with or without SVR

Statistics	Sex (p)	Age (p)	ALT (p)	HCV RNA (p)	Cirrhosis (p)
Mann-Whitney U	0,593	0,088	0,593	0,435	0,275

It was studied correlation between SVR and baseline factors before treatment (tab. 4).

Table 4. Correlation between SVR and baseline factors.

	Spearman correlation	P value
Sex	r = -0,064	p = 0,597
Age	r = 0,204	p = 0.088
ALT	r = -0,064	p = 0.597
HCV RNA	r = -0,093	p = 0.439
Cirrhosis	r = 0,300	p = 0,278

The patients' gender, age, baseline ALT and HCV RNA, presents of liver cirrhosis were not predictor of SVR in our group of patients with chronic HCV genotype 1 infection.

We analyzed correlation between SVR and EVR in our group of patients (tab. 5).

Table 5. Correlation between SVR and EVR.

	Spearman correlation	P value
EVR	r = 0,759	p = 0,011

There were a strong correlation between EVR and SVR. The virological response at the end of 12 weeks SoC therapy predicted much better achieving of SVR than the baseline viral and host factors.

DISCUSSION

Pretreatment predictors of response are useful for advising patients on their likelihood of an SVR. Absence of favorable factors should not be used, however, to deny therapy. Data on predictor of an SVR come from several sources: registration trials which have strict inclusion and exclusion criteria and may not accurately reflect the general population infected with HCV and community-based trials that may not be conducted with same rigor as registration trials.

Multivariate analyses have identified two major predictors of an SVR among all population studied: the viral genotype and pretreatment viral load (10, 11, 12). Our results did not confirm the importance of baseline HCV RNA levels for achieving SVR when single nonparametric analysis was used. This conclusion is supported by the last EASL Clinical Practice Guidelines for management of HCV infection (9). There was pointed that the strongest baseline predictors of SVR were: HCV genotype; genetic polymorphisms located in chromosome 19 (IL28B) and stage of liver fibrosis. In our studied group the number of patients with advance fibrosis

(liver cirrhosis) is relatively low – 13%. This could explain the absence of correlation between SVR and present of liver cirrhosis in our treated population. Other possible explanation for low number of cirrhotic patients in our group was their young age – 31 years. This defined short duration of HCV infection. The high rate of SVR – 80% was likely due to low prevalence of cirrhosis and young age of our patients. The sex of patients was not independent predictor of SVR according the results of our treatment.

This study very clear showed the advance of viral response during SoC therapy above baseline viral and host factors to predict SVR. EVR significantly correlated with SVR. According the new EASL Clinical Practice Guidelines for management of HCV infection EVR defined 48 weeks treatment with SoC in patients infected with HCV genotype 1 (13). Treatment for all HCV genotypes should be stopped at week 12 if the HCV RNA decrease is less than 2 log10 IU/ml. All this determinates that during SoC treatment, HCV RNA measurements should be performed more often during the first 3 months to help tailor treatment.

CONCLUSION

The viral response during the first 3 months of PEG-IFN alpha and RBV therapy in patients with chronic HCV genotype 1 infection is the strongest independent predictor among the others baseline viral and host factors for achieving of SVR.

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