

Original article

Predictors of sustained virological response in patients with hepatitis C virus genotype 3 infection

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Abstract

Aim of the study: To assess predictors of sustained virological response (SVR) in patients with chronic hepatitis C virus (HCV) genotype 3 treated with standard therapy.

Material and methods: We retrospectively investigated data of 116 consecutive treatment-naïve patients chronically infected with HCV genotype 3, treated with pegylated interferon alpha (PegIFN α) and ribavirin (RBV) for 24 weeks. HCV RNA at week 4 (rapid virological response – RVR) and week 12 (early virological response – EVR) were measured in 85 and 105 patients respectively. Liver biopsy data were available for 103 patients. The variables were compared between patients with an SVR and those without.

Results: Overall 70.7% of patients achieved an SVR. Pretreatment factors including younger age, mild liver fibrosis as well as normal values of gamma-glutamyl transferase (GGT) and platelet count were significantly associated with higher SVR rate in univariate analysis. In the multivariate analysis only baseline platelet count > 140 000/ μ l and normal GGT activity were correlated with higher SVR rate. At weeks 4 and 12 HCV RNA was undetectable in 34.1% and 84.8% of patients respectively. The SVR rate was significantly higher in patients with an RVR compared to those without ($p = 0.002$). Only 2 patients with a rapid and early virological response did not achieve an SVR; both had negative pretreatment prognostic factors.

Conclusions: In treatment-naïve patients with genotype 3 HCV infection, low baseline platelet count and elevated GGT activity were significantly associated with poor response to PegIFN α and RBV. Achieving a rapid and early virological response was associated with higher likelihood of an SVR.

Key words: hepatitis C, antiviral treatment, genotype 3.

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Introduction

Hepatitis C virus (HCV) infection is thought to be a major public health issue worldwide. An estimated 3% of the global population is infected with HCV. Infection of genotype 1 is the most common, but in some regions, including Southern Asia, Australia, some western Europe countries and Russia, genotype 3 is also frequent. Among Polish patients with chronic hepatitis C (CHC) prevalence of GT3 was assessed at 13.8% compared with 79.4% of GT1 [1]. It is increasingly recognized that genotype 3 infection is associated

with higher probability of liver steatosis, accelerated fibrosis progression towards cirrhosis and greater risk of hepatocellular carcinoma compared to other HCV genotypes [2, 3]. The combination treatment with pegylated interferon alpha (PegIFN α) and ribavirin (RBV) has been a standard of care for chronic hepatitis C since 2000. Hepatitis C virus genotype is one of the most important predictors of treatment outcome. The PegIFN α /RBV therapy resulted in a sustained virological response (SVR) in approximately 50% of patients infected with GT1 and 4, whilst efficacy estimated altogether for patients with GT2 and 3 exceeded 75%,

so they were called “easy-to-treat” [4-7]. Separate analysis for patients infected with genotype 3 demonstrated lower effectiveness of the standard therapy, especially in those with liver cirrhosis, patients without a rapid virological response and treatment experienced [8].

In the last few years development of direct acting antiviral drugs (DAAs), used with or without PegIFN α , dramatically changed the management of HCV infection. Unfortunately, improvement of the treatment efficacy for genotype 3 is not so spectacular as for other genotypes of infected patients. Available data indicate that in the era of novel CHC therapies genotype 3 became the most difficult to treat [8-11].

The purpose of this study was to investigate pre- and on-treatment predictors associated with sustained virological response in a single-center population of patients with chronic hepatitis C virus GT3 treated with standard therapy. The availability of new therapeutic regimens for genotype 3 patients is still insufficient, and their efficacy is unsatisfactory as well, so this analysis was performed to find out how we can optimize the strategy of treatment with PegIFN α and RBV.

Material and methods

Materials

The retrospective cohort study included 116 consecutive treatment-naïve adult patients (54 men and 62 women, 18-70 years old) chronically infected with HCV genotype 3. Patients were consecutively treated at the Infectious Diseases Unit of the Regional Polyclinic Hospital from January 2003 to December 2014. The diagnosis of chronic HCV infection was based on positive testing for serum anti-HCV markers and HCV RNA, and was confirmed by liver biopsy in 103 patients.

Patients received PegIFN 2a or alpha 2b plus RBV for 24 weeks. Interferon was dosed according to product characteristics, and RBV was given in a flat (800 mg) or weight-based dose (1000 mg/d in patients \leq 75 kg and 1200 mg/d in patients $>$ 75 kg).

Patients with concomitant HBV infection (all anti-HBc-positive patients were negative for HBsAg and HBV DNA), HIV infection, or autoimmune liver diseases were excluded from the analysis. Therapy was started after 6 months of alcohol abstinence.

Methods

Demographic and laboratory data were collected for all patients at the start of treatment.

Alanine aminotransferase (ALT) and gamma-glutamyl transferase (GGT) activities were assayed by conventional methods.

Cryoglobulins were detected by the precipitation method: collecting the serum samples and separating at 37°C, then keeping at 4°C for 7 days for the presence of cryoprecipitate.

Antibodies for HCV were performed by a third-generation enzyme-linked immunoassay (ELISA).

HCV RNA was tested by the RT-PCR method based on COBAS AMPLICOR HCV v. 2.0 (Roche Diagnostic Inc.). The lower limit of detection was 30 IU/ml. HCV genotype was determined by a hybridization method (InnoLipa HCV, Innogenetics).

Serum HCV RNA was assessed in all patients at baseline (quantitative results were available for 98 patients), then at weeks 4, 12 and at the end of treatment during the therapy period. A rapid virological response (RVR) was defined as undetectable serum HCV RNA level by week 4 of therapy, and early virological response (EVR) was defined as undetectable HCV RNA after 12 weeks of treatment.

HCV RNA at week 4 and week 12 was assessed in 85 and 105 patients respectively.

The efficacy end point was sustained virological response, defined as undetectable HCV RNA at 24 weeks after the end of treatment.

Liver biopsy data were available for 103 patients within 12 months prior to antiviral therapy. Histological evaluation was carried out according to the Ishak classification system.

The variables were compared between patients with an SVR and those without as follows: age, gender, body mass index, stage of fibrosis, presence of cryoglobulins, HCV RNA viral load at the beginning of the therapy, presence of aHBc total, type of PegIFN α , dose of RBV (flat or weight-based) and selected laboratory parameters.

The study was performed in accordance with the latest version of the Declaration of Helsinki and approved by the local Ethics Committee; all patients signed a written consent form.

Statistical analysis

Quantitative data were presented as median (together with lower and upper quartiles) and qualitative data were characterized by number and percentage distribution. Factors associated with higher SVR rate were assessed by uni- and multivariate logistic regression analyses. Statistical significance was accepted as $p < 0.05$.

Results

Of the 116 treatment-naïve adult patients included in the analysis, mean age was 43 ± 14.4 years, and male-to-female ratio was 0.87/1 (54/62). Liver biopsy data were available for 103 patients; 25 of them (24.3%) presented significant liver fibrosis (stage 3-6 in Ishak score). Only 6 patients (5%) were defined with liver cirrhosis (stage 5-6 in Ishak score). The demographic, laboratory and clinical characteristics of the patients at baseline are presented in Table 1.

Pegylated interferon and RBV were started in all patients, but in 11 (9.5%) therapy was discontinued, in 10 patients because of adverse events and in 1 according to virological stopping rules (no decline of viremia at week 12). The most frequent adverse event leading to treatment discontinuation was neutropenia, observed in 4 patients (defined as absolute neutrophil count < 0.5 G/l). The remaining reasons for therapy cessation were anemia with hemoglobin level < 8.5 g/dl and thrombocytopenia with platelet count < 30 G/l, vision impairment, chest pain, depressive disorder and pulmonary sarcoidosis. All patients who required drug discontinuation were non-responders. Week 4 HCV RNA was undetectable in 29/85 patients (34.1%), 17 females and 12 males. Early virological response was achieved by 89/105 patients (84.8%), 46 females and 43 males. At the end of the treatment negative HCV RNA was noted in 92/116 (79.3%) patients, and relapse was observed in 10 patients (11%) in the follow-up period. Overall 82/116 (70.7%) patients achieved sustained virological response. Among patients with an SVR there were 43 females and 39 males.

Pre-treatment factors including younger age, mild liver fibrosis (< 3 points in Ishak's score) as well as normal values of GGT and platelet count were significantly associated with higher SVR rate in univariate analysis. In the multivariate logistic regression analysis only pre-treatment platelet count $> 140\ 000/\mu\text{l}$ (adjusted OR = 9.6, 95% CI: 2.8-33.9, $p < 0.001$) and normal GGT activity were correlated with higher SVR rate (adjusted OR = 3.5, 95% CI: 1.3-9.4, $p = 0.02$). Statistical analysis of baseline factors potentially associated with sustained virological response is presented in Table 2.

Analysis performed in the subgroup of patients with liver biopsy ($n = 103$) also confirmed that baseline factors including younger age, mild liver fibrosis (< 3 points in Ishak's scale), normal values of GGT and platelet count were significantly associated with higher SVR rate in univariate analysis.

In the multivariate logistic regression analysis only pre-treatment platelet count $> 140\ 000/\mu\text{l}$ ($p = 0.013$) and normal GGT activity ($p = 0.015$) were correlated with higher SVR rate, whereas younger age ($p = 0.49$)

Table 1. Baseline characteristics of analyzed group ($n = 116$)

Characteristic	Value*
Male	54 (46.6%)
Age, years	43 (27-51)
Body mass index > 25 kg/m ²	55 (47.4%)
Low pretreatment viral load ($n = 98$) $< 400\ 000$ IU/ml	45 (46%)
RBV dose	
Flat	98 (84.5%)
Weight-based	18 (15.5%)
ALT IU/L	89 (57-141)
GGT IU/L	
Female	33 (21-48)
Male	55 (30-88)
Platelets $\times 10^9/\text{l}$	185 (153-222)
anti-HBc total (+)	23 (19.8%)
Fibrosis stage ($n = 103$)	
Ishak score 0-2	78 (75.7%)
Ishak score 3-6	25 (24.3%)
Cryoglobulins positive	48 (41.3%)
PegIFN α 2a	40 (34.5%)
PegIFN α 2b	76 (65.5%)

*Median (Q1-Q3) for quantitative data and n (%) for qualitative data

and mild liver fibrosis ($p = 0.19$) were statistically non-significant (Table 3).

At week 4 HCV RNA results were available for 85 patients, and 29 of them (34.1%) achieved a rapid virological response. The RVR rate was significantly higher in patients with an SVR compared to those without (44.3% [27/61] vs. 8.3% [2/24], $p = 0.002$) (Table 3).

HCV RNA week 12 assessment was performed in 105 patients; an early virological response was observed in 89 patients (84.8%). The EVR rate was significantly higher among patients who achieved an SVR compared to those who did not (95.1% [77/81] vs. 50.0% [12/24], $p < 0.00001$).

Both rapid and early virological responses were observed in 80 patients. No combination of RVR/no EVR was observed. The combination of both RVR/EVR was observed in 44.3% of patients (27/61) who achieved an SVR and in 10.5% (2/19) of patients without a sustained response ($p = 0.007$). The combination of no RVR/EVR was noted in 49.2% of patients (30/61) who achieved an SVR and in 36.8% of patients (7/19) without a sustained virological response ($p = 0.43$).

There was no significant difference in frequency of low platelet count between patients with an RVR

Table 2. Pre-treatment factors potentially associated with sustained virological response

Parameter*	No SVR (n = 34)	SVR (n = 82)	Univariate OR [95%CI]	Univariate p-value	Multivariate OR [95%CI]	Multivariate** p-value
Age ^a						
< 43 years	10 (29.4)	49 (59.8)	3.6 [1.5-8.4]	0.004	1.9 [0.7-5.1]	0.22
≥ 43 years	24 (70.6)	33 (40.2)	1		1	
Sex						
Female	19 (55.9)	43 (52.4)	1			
Male	15 (44.1)	39 (47.6)	1.1 [0.5-2.6]	0.74		
BMI						
< 25 kg/m ²	15 (44.1)	46 (56.1)	1.6 [0.7-3.6]			
≥ 25 kg/m ²	19 (55.9)	36 (43.9)	1	0.24		
anti-HBc						
Positive	9 (26.5)	14 (17.1)	1			
Negative	25 (73.5)	68 (82.9)	1.7 [0.7-4.5]	0.25		
PegIFN α						
2a	9 (26.5)	31 (37.8)	1.7 [0.7-4.1]	0.25		
2b	25 (73.5)	51 (62.2)	1			
Cryoglobulins						
Positive	17 (50.0)	31 (37.8)	1	0.23		
Negative	17 (50.0)	51 (62.2)	1.6[0.7-3.7]			
ALT activity						
Normal	6 (17.6)	19 (23.2)	1.4 [0.5-3.9]	0.51		
Elevated	28 (82.4)	63 (76.8)	1			
GGT activity						
Normal	14 (41.2)	58 (70.7)	3.5 [1.5-7.9]	0.004	3.5 [1.3-9.4]	0.02
Elevated	20 (58.8)	24 (29.3)	1		1	
RBV dose						
Flat	27 (79.4)	71 (86.6)	1.7 [0.6-4.7]	0.33		
Weight-based	7 (20.6)	11 (13.4)	1			
Viral load (n = 98), IU/ml						
< 400 000	14 (48.3)	31 (44.9)	1	0.76		
≥ 400 000	15 (51.7)	38 (55.1)	1.1 [0.5-2.7]			
Platelets						
Below normal	14 (41.2)	6 (7.3)	1	0.0001	1	< 0.001
Normal	20 (58.8)	76 (92.7)	8.9 [3.0-26.0]		9.6 [2.8-33.9]	
Stage (n = 103), Ishak score						
S0-2	16 (55.2)	62 (83.8)	4.2 [1.6-10.9]	0.003		
S3-6	13 (44.8)	12 (16.2)	1			

*Variables expressed as n (%)

**Only variables with p-value < 0.05 in univariate analysis were assessed.

^a Criterion of division was median value

and without an RVR in the group with both virological assessments ($p = 1$). However, low platelet count was significantly more frequently observed in patients without EVR compared to those with an early virological response (35.7% [5/14] vs. 10.6% [7/66], $p = 0.03$). The frequency of elevated GGT activity was similar in patients with an RVR and without, as well as in patients with EVR and without ($p = 0.23$) in the group with both virological data.

All 29 patients with an RVR also had negative HCV RNA at week 12. Finally, 2 of them did not achieve

a sustained virological response (6.8%); 1 had liver cirrhosis and a low pretreatment platelet count and the other had elevated pretreatment GGT activity. Twelve of 89 patients (13.5%) with negative HCV RNA at week 12 did not achieve an SVR. There was a significant difference between the rate of patients who at baseline presented elevated GGT activity and a low platelet count in the group without an SVR compared to 77 patients who finally achieved a sustained virological response (respectively 8/12 vs. 23/77, $p = 0.02$ and 4/12 vs. 6/77, $p = 0.03$).

Table 3. Patients with biopsy ($n = 103$): pre-treatment factors potentially associated with sustained virological response

Parameter*	No SVR ($n = 29$)	SVR ($n = 74$)	Univariate OR [95%CI]	Univariate p -value	Multivariate OR [95%CI]	Multivariate** p -value
Age ^a						
< 43 years	9 (31.0)	42 (56.8)	2.9 [1.2-7.3]	0.02	1.5 [0.5-4.3]	0.49
≥ 43 years	20 (69.0)	32 (43.2)	1		1	
Sex						
Female	17 (58.6)	37 (50.0)	1			
Male	12 (41.4)	37 (50.0)	1.4 [0.6-3.4]	0.43		
BMI						
< 25 kg/m ²	13 (44.8)	42 (56.8)	1.6 [0.7-3.8]			
≥ 25 kg/m ²	16 (55.2)	32 (43.2)	1	0.28		
anti-HBc						
Positive	7 (24.1)	13 (17.6)	1			
Negative	22 (75.9)	61 (82.4)	1.5 [0.5-4.2]	0.45		
PegIFN α						
2a	7 (24.1)	26 (35.1)	1.7 [0.6-4.5]	0.29		
2b	22 (75.9)	48 (64.9)	1			
Cryoglobulins						
Positive	15 (51.7)	25 (33.8)	1	0.10		
Negative	14 (48.3)	49 (66.2)	2.1 [0.9-5.0]			
ALT activity						
Normal	6 (20.7)	19 (25.7)	1.3 [0.5-3.7]	0.60		
Elevated	23 (79.3)	55 (74.3)	1			
GGT activity						
Normal	13 (44.8)	54 (73.0)	3.3 [1.4-8.1]	0.009	3.6 [1.3-10.1]	0.015
Elevated	16 (55.2)	20 (27.0)	1		1	
RBV dose						
Flat	24 (82.8)	65 (87.8)	1.5 [0.5-4.9]	0.50		
Weight-based	5 (17.2)	9 (12.2)	1			
Viral load, IU/ml						
< 400 000	15 (51.7)	39 (52.7)	1.04 [0.4-2.5]	0.93		
≥ 400 000	14 (48.3)	35 (47.3)	1			
Platelets						
Below normal	10 (34.5)	6 (8.1)	1	0.002	1	0.013
Normal	19 (65.6)	68 (91.9)	6.0 [1.9-18.5]		5.3 [1.4-19.7]	
Stage, Ishak score						
S0-2	16 (55.2)	62 (83.8)	4.2 [1.6-10.9]	0.003	1	0.19
S3-6	13 (44.8)	12 (16.2)	1		2.2 [0.7-6.9]	

*Variables expressed as $n(\%)$ **Only variables with p value < 0.05 in univariate analysis were assessed.^a Criterion of division was median value among all 116 patients.

Discussion

In the present study 82/116 (70.7%) treatment-naïve patients infected with GT3 HCV achieved a sustained virological response on dual therapy consisting of PegIFN α and RBV. The efficacy of 24 weeks of treatment was comparable to most other reports from clinical trials and real-life studies, where the SVR rate was estimated to be between 60 and 90% [4, 6, 7, 12-21]. The lower SVR rate was documented by Niederau *et al.* in a large community-based multicenter cohort of

1956 GT3 treatment-naïve patients treated with standard therapy; 56.9% of them achieved a sustained virological response [21]. An even worse treatment result was observed by Cheetham *et al.* in a group of 484 patients infected with genotype 3 HCV, treated with PegIFN α and RBV with a 52% SVR rate, probably due to the high number of patients with advanced liver fibrosis and cirrhosis in the cohort [22].

The aim of the current analysis was to assess pre- and on-treatment factors associated with higher likelihood of an SVR. By univariable logistic regression

analysis we revealed that younger age, non-significant liver fibrosis, GGT activity and platelet count in the normal range were positive predictors of treatment success. However, multivariable logistic regression analysis identified only normal platelet count and GGT activity as independent predictors of a sustained virological response.

Several studies have supported our findings that younger patients chronically infected with GT3 are more likely to achieve an SVR during therapy with interferon and RBV [6, 13, 14, 23-26].

To define the predictive value of biochemical parameters we assessed the potential link between baseline ALT, GGT activity and response to antiviral treatment, and only GGT level was found to be correlated highly with SVR as an independent factor; these results are consistent with those reported by other investigators [12, 16, 27]. We did not confirm the correlation between pretreatment ALT level and sustained virological response observed by some investigators [6, 25, 27].

There is a small number of studies describing platelet count as a predictor of treatment outcome in genotype 3 patients. Our findings that baseline subnormal platelet count was associated with significantly lower SVR rate compared with normal values are supported by those reported by Innes *et al.* [12] as well as the multinational PROPHESYS study results [20]. The present study demonstrated a substantial difference in the sustained virological response rate between patients with no and significant liver fibrosis by univariate logistic analysis (79.5% vs. 48%, $p = 0.003$). The presence of significant liver fibrosis and cirrhosis has long been recognized to be associated with lower probability of treatment success in GT3 patients; our conclusions concerning mild liver fibrosis as a favorable factor are in agreement with those reported by many other investigators [5, 6, 15, 19, 23].

Among viral baseline factors most of the literature has noted a positive link between pretreatment HCV RNA levels and SVR likelihood in PegIFN α and RBV therapy of GT3 HCV infection. In the present study we divided patients into two subgroups according to viral load at the start of treatment, one group with 400 000 IU/ml HCV RNA and the second with equal or above this value. There are controversial reports concerning pretreatment HCV RNA viral load below and above 400 000 IU/ml. Shiffman *et al.* documented a significantly better treatment outcome for baseline HCV RNA < 400 000 IU/ml, for both 16- and 24-week therapy regimens, in patients infected with GT2 and 3 HCV, but the analyzed cohort was more numerous (737 patients infected with genotype 3) compared to ours [6]. On the other hand, Niederau *et al.* did not find this factor to be a positive predictor

of SVR in univariate logistic analysis; these results supported our findings [21]. Of note, our data about no link between baseline HCV viral load and SVR rate are also confirmed by the results of a study performed by Cheetham *et al.* [22].

Although baseline factors have been useful for predicting the treatment outcome, the most valuable predictor of SVR described in the literature is the rapid virological response. In agreement with other reports, our data suggested that an RVR is highly predictive of a sustained virological response [4, 6, 7, 16, 18, 24, 27]. In the present cohort the rate of negative HCV RNA results at week 4 was significantly higher in patients with an SVR compared to those without (44.3% vs. 8.3%). In the current analysis an RVR was achieved by 34.1% of patients; it is a much lower rate than reported by above-cited investigators. Our RVR data were limited to 73% of the analyzed cohort, and that fact could be one of the more likely possible explanations of this discrepancy. Moreover, no study has yet been conducted in Poland to assess the treatment outcome in patients with chronic hepatitis C infected with genotype 3, and no data of the RVR rate in this population are available to compare with our findings. Results from Polish centers were only a part of multinational studies with no separate analysis [20, 32]. Therefore, to explore possible demographic and geographical differences and answer the question of on-treatment response in Polish GT3 patients, further research is needed.

Although RVR is considered to be the strongest factor determining treatment success, another viral kinetics parameter has proven useful for prediction of therapy outcome: negative HCV RNA at week 12. In the current study EVR results were available for 105/116 (90.5%) patients and 84.8% of them achieved an early virological response, defined as above. Probably due to insufficient data, our EVR results are lower compared to those reported by other investigators [29, 32, 33]. In agreement with some other reports, our data suggested a positive link between early and sustained virological response; the EVR rate was significantly higher among patients who finally achieved an SVR compared to those who did not (95.1% vs. 50.0%) [25, 29, 33].

Finally, we assessed the role of RBV dosing for SVR likelihood. The issue of whether a higher, weight-based RBV dose compared to a flat dose can result in a better treatment outcome in GT3 patients was the subject of analysis. We did not find an impact of RBV dose on probability of achieving an SVR; our results have been confirmed by other investigators, reporting no benefit of a higher RBV dose [4, 16].

Although this analysis was carefully prepared, several limitations should be considered when interpret-

ing our findings. First, the retrospective design of this study relied on data that had already been gathered. Second, the number of patients was relatively small, and it resulted in ORs with a large confidence interval on one hand and no statistical significance reached for some factors on the other. Third, for some patients we had no RVR or EVR data; insufficient information could affect the final results.

Conclusions

In our study over 70% of patients chronically infected with genotype 3 HCV achieved a sustained virological response during standard therapy. We found low pre-treatment platelet count and elevated GGT activity to be significantly associated with poor response to PegIFN α and RBV therapy. Achieving a rapid and early virological response can efficiently predict SVR.

Disclosure

Authors report no conflict of interest.

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