HEPATITIS C THERAPY-RELATED HAEMATOLOGICAL SIDE EFFECTS ARE ASSOCIATED WITH TREATMENT OUTCOME

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HEMATOLOŠKA NEŽELJENA DEJSTVA TERAPIJE HEPATITISA C SU POVEZANA SA ISHODOM LEČENJA

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ABSTRACT

Treatment of patients suffering from chronic hepatitis C with standard pegylated interferon alpha 2a plus ribavirin has limited efficacy. Therapy outcome is dependent on several factors of both the host and virus, including age, sex, stage of fibrosis, viral genotype, viral load, and occurrence of haematological adverse events during chronic hepatitis C treatment. The aim of this study was to determine the relationship between the viral and host factors and the haematological side effects of therapy with sustained virological response.

Fifty-four patients were treated with combined pegylated interferon alpha 2a plus ribavirin therapy. Hepatitis C virus genotyping, viral load, histopathological liver changes and biochemical parameters were evaluated for each patient before beginning treatment. Each patient's blood count was analysed during each clinical visit.

Sustained virological response was achieved in 75,9% of patients. Baseline AST and ALT levels were significantly higher in patients with a poor response to therapy (p<0,05). Other clinical and laboratory parameters did not reach statistical significance. Both responders and non-responders developed anaemia. A decrease in thrombocytes, neutrophils and white blood cells was significantly associated with a sustained response to therapy (p<0,05, p<0,05 and p<0,001, respectively).

Sustained virological response was associated with lower baseline AST and ALT values and thrombocytopenia, leucopenia and neutropenia at the end of the treatment. All treated patients developed anaemia.

Keywords: *chronic hepatitis C, pegylated interferon alpha 2a, ribavirin, anaemia, thrombocytopenia, leucopoenia, neutropenia*

SAŽETAK

Standardna terapija hronične HCV infekcije, primenom pegiliranog interferona alfa 2a i ribavirina, ima ograničenu efikasnost. Na ishod terapije utiču brojni faktori domaćina i virusa: starost, pol, stadijum fibroze, genotip virusa, nivo bazalne viremije, ali i pojava neželjenih efekata terapije. Cilj ovog istraživanja je bio da se utvrdi povezanost neželjenih hematoloških efekata terapije i trajnog virusološkog odgovora kod pacijenata sa hroničnom HCV infekcijom.

Ispitivanjem je bilo obuhvaćeno 54 bolesnika sa hroničnim HCV hepatitisom. Lečenje je sprovedeno tokom 24/48 nedelja, u zavisnosti od genotipa virusa. Svim bolesnicima su pre početka terapije određivani bazalni nivo viremije, genotip virusa, stepen histopatoloških promena u jetri i biohemijski parametri, dok je kompletna krvna slika je određivana prema standardnom protokolu tokom i nakon završetka terapije.

Trajni viroloski odgovor postignut je u 75,9% pacijenata. Bazalni nivo AST-a i ALT-a je bio značajno veći kod pacijenata sa slabim odgovorom na terapiju (r <0,05). Drugi klinički i laboratorijski parametri nisu dostigli statističku značajnost. Anemija se razvila u obe grupe ispitanika, i u grupi respondera ali i u grupi non-respondera. Smanjenje broja trombocita, neutrofila i leukocita je bilo značajno povezano sa dobrim odgovor na terapiju (r <0,05, r <0,05 i r <0,001).

Utvrđeno je da je trajni virusološki odgovor povezan sa nižim vrednostima AST i ALT, trombocitopenijom, leukocitopenijom i neutropenijom na kraju tretmana. Kod svih lečenih pacijenta javila se anemija.

Ključne reči: *hronični hepatitis C, pegilovani interferon alfa 2a, ribavirin, anemija, trombocitopenija, leukopenija, neutropenija.*

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INTRODUCTION

Hepatitis C infection is a leading cause of chronic liver disease, fibrosis and liver cirrhosis, which leads to hepatocellular carcinoma in 1-5% of cases (1, 2). In approximately 75% of patients, acute hepatitis C evolves to chronic disease (3). The current standard treatment of hepatitis C is pegylated interferon alpha 2a (PEG-IFNα-2a) and ribavirin (RBV) (4). However, this therapy has limited efficacy and is successful in only 55-80% of patients. Several studies have been conducted to identify factors that influence therapy outcome. Previous studies have been conflicting, as the size and composition of the studied groups varied. Achieving sustained virological response (SVR) depends on many factors, such as HCV genotype, viral load, age, gender, genetics and patient ethnicity, degree of histopathological liver changes and infection duration (5, 6). However, combined PEG-IFNα-2a+RBV therapy has diverse side effects that are similar to flu-like symptoms, including fever, headache, cough, nausea, and haematological disorders (7). Some of these adverse effects can be severe and require modification of the therapy dosage or withdrawal from therapy. However, a previous study by Pawlowska et al. showed that alterations in haematological parameters are associated with response to therapy (8).

Therefore, the aim of our investigation was to determine the relationship between various viral and host factors and haematological side effects in response to PEG-IFNα-2a+RBV therapy in chronic HCV patients.

PATIENTS AND METHODS

A retrospective study was conducted of 76 patients with chronic hepatitis C infection who completed combined PEG-IFNα-2a+RBV therapy in the Clinic for Infectious Diseases, Clinical Centre of Kragujevac, from January 2007 to December 2010. Of the 76 patients who started therapy, 22 failed to return for follow-up evaluation of blood count; therefore, a total of 54 patients with complete blood count follow-up were reviewed. The study was approved by the local Ethics Committee, and written informed consent was obtained from all patients in accordance with the Declaration of Helsinki. Anamnesis, laboratory data, liver biopsy, serum HCV viral load and genotyping were obtained for each patient prior to therapy. The degree of histopathological changes in the liver was determined by Haematoxylin-Eosin staining of biopsy specimens. Blood count and haemoglobin were assessed during each clinical visit.

Patients infected with HCV genotypes 1 and 4 were treated with PEG-IFNα-2a (180 μg/week) and ribavirin (800-1200 mg/day) for 48 weeks, whereas patients infected with HCV genotypes 2 or 3 completed the same treatment for 24 weeks. Sustained virological response (SVR) was defined as undetectable HCV RNA 24 weeks after therapy. If HCV RNA was steadily detectable during and at the end of therapy, patients were defined as non-responsive to therapy (NR), whereas the reappearance of viral RNA in patients whose serum HCV RNA had been undetectable was categorized as a relapse (relapse responders [RR]).

Clinically relevant cut-offs were defined as follows: leucopoenia (WBC less than $4x10^9$ cells/L) neutropenia (neutrophils less than $1.5x10^9$ cells/L) thrombocytopenia (platelets less than $135x10^9$ cells/L) and anaemia (haemoglobin less than 120 g/L for women and less than 130 g/L for men; erythrocytes less than $3.86x10^{12}$ cells/L for women and $4.34x10^{12}$ cells/L for men). The PEG-IFNα-2a dose was reduced for patients with neutrophil counts $<0.75x10^9$

Table 1. Baseline demographic and clinical characteristics and laboratory data of the study population

Characteristics	*Total (n=54)*
Male gender, n (%)	36 (66,7)
Age, years, mean±SD	41.1±13.4
Baseline HCV RNA ($x10^6$ IU/ml±SD)	8.1±12.9
HCV genotypes, n (%)	
G1	31 (57.4)
G2	1 (1.9)
G3	21 (38.9)
G4	1 (1.9)
Liver biopsy results (fibrosis), n (%)	
F0	6 (11.1)
F1	26 (48.1)
F2	12 (22.2)
F3	6 (11.1)
F4	4 (7.4)
Risk factor for acquiring HCV, n (%)	
IDU	22 (40.7)
Blood transfusion	12 (22.2)
Perinatal Infection	1 (1.9)
Sexual partners with HCV	1 (1.9)
Unknown factors	18 (33.3)
Treatment response rate	
SVR/ETR	41 (75.9)
NR/RR	13 (24.1)
Biochemical parameters, mean±SD	
AST (IU/l)	115.5±52.0
ALT (IU/l)	149.4±58.4
AF (IU/l)	66.1±17.9
AFP1 (ng/ml)	3.9±3.1
Bilirubin unconjugated (μmol/l)	10.8±4.0
Bilirubin conjugated (μmol/l)	2.7±1.4
Blood Proteins (g/l)	73.0±5.7
Albumins (g/l)	45.7±3.9
Globulins (g/l)	27.6±6.9
INR (s)	1.0±0.1
Triglycerides (mmol/l)	1.3±0.7
Cholesterol (mmol/l)	4.3±1.1

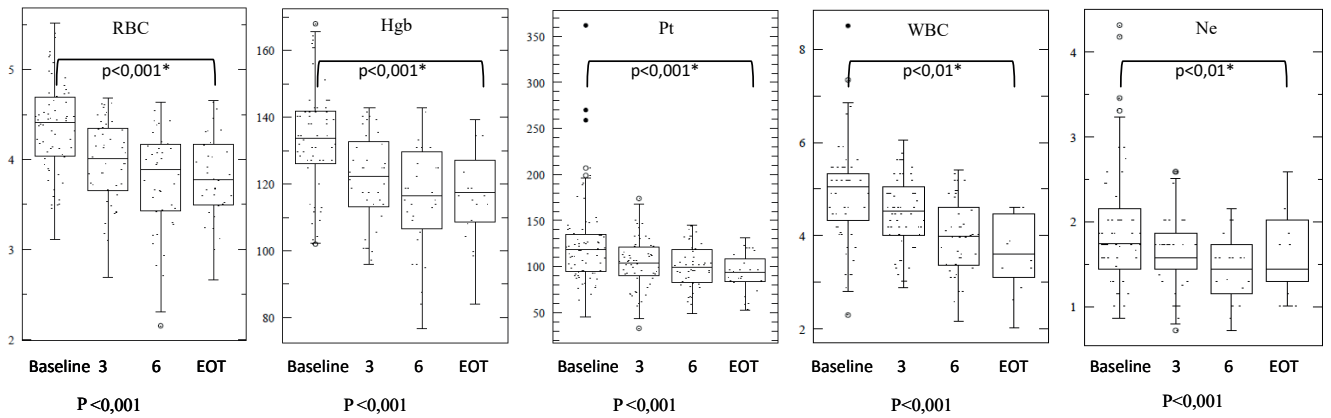

Figure 1. Complete blood count determined before treatment (baseline), 3 and 6 months after beginning treatment and at the end of therapy (EOT). P values were determined using ANOVA for differences in values during treatment. *Statistical differences between the baseline and EOT time points were determined using a Mann-Whitney U-test.

cells/L and platelet counts <50x10^9 cells/L and was withheld for patients with absolute neutrophil counts <0.5x10^9 cells/L and platelet counts <25x10^9 cells/L. Ribavirin doses were modified for patients with a haemoglobin concentration <100 g/L and was withheld for patients with a haemoglobin concentration <85 g/L.

All statistical analyses were conducted using commercial SPSS software (version 19.0, SPSS Inc., Chicago, IL). Collected data were stratified by subgroups of patients of interest and analysed using central tendency, variability and frequency. Contingency Tables were used to analyse the relationship between two or more variables. The distributions of data were evaluated for normality using the Kolmogorov-Smirnov test. Quantitative parametric data were compared between two study groups using an unpaired t-test. A Mann-Whitney U-test and Kruskal-Wallis test were used for comparative analysis between groups of non-parametric data. For analysis of the association between haematological parameters and therapy response, logistic regression and multivariate analysis were performed. A p-value of <0.05 was considered statistically significant.

RESULTS

The majority of the patients were male (67%), and the average patient age was 41,1±13,4 years (Table 1). The median HCV-RNA viral load was 8,1±12,9x10^6 IU/ml. HCV genotype 1 was dominant (57,4%), while genotype 3 was present in 38,9% of patients and genotypes 1 and 4 were present in 1,9% of patients each. The major route of infection was injection drug use (40,7%), followed by blood transfusion (22,2%); in 33,3% patients, the virus transmission route was unknown. Liver fibrosis was present in 88,9% of patients, primarily at the F1 (48,1%) or F2 stage (22,2%). The majority of patients achieved sustained virological response (SVR) (75,9%), and 24,1% patients showed poor response to therapy (RR and NR). Laboratory data of patients are presented in Table 1. Haematological parameters during follow-up visits showed a significant decrease in haemoglobin (Hgb) levels and in the count of red blood cells (RBC), platelets (Pt), white blood cells (WBC) and neutrophils (Ne) (p<0,001) during therapy (Figure 1).

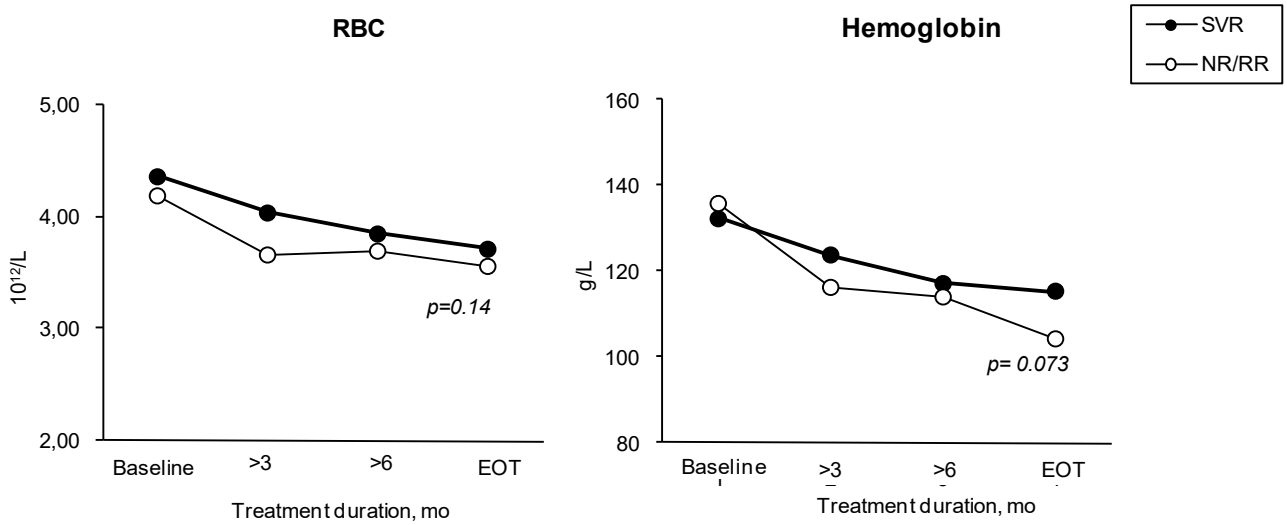

Figure 2. Median erythrocyte count and haemoglobin levels in the SVR and NR/RR groups before treatment (baseline), 3 and 6 months after beginning treatment and at the end of therapy (EOT);
*Differences between SVR and NR EOT time points were determined using a Mann-Whitney U-test.

Table 2. Comparison of demographic and clinical characteristics and laboratory data between patients with or without sustained virological response. * p<0.05

Characteristics	*NR/RR (n=13)*	*SVR (n=41)*
Male gender, n (%)	10 (76.9)	25 (61.0)
Age, years, mean±SD	42.1 ± 12.3	40.8±14.5
Baseline HCV RNA (x10^6 IU/ml±SD)	6.2±8.9	8.6±13.9
HCV genotypes, n (%)		
G1	9 (69.2)	22 (53.7)
G2	1 (7.7)	0 (0)
G3	3 (23.1)	18 (43.9)
G4	0 (0)	1 (2.4)
Liver biopsy results (fibrosis), n (%)		
F0	2 (15.4)	4 (9.8)
F1	5 (38.5)	21 (51.2)
F2	2 (15.4)	10 (24.4)
F3	3 (23.1)	3 (7.3)
F4	1 (7.7)	3 (7.3)
Risk factor for acquiring HCV, n (%)		
IDU	4 (30.8)	18 (43.9)
Blood transfusion	3 (23.1)	9 (22.0)
Perinatal Infection	0 (0)	1 (2.4)
Sexual partners with HCV	1 (7.7)	0 (0)
Unknown factors	5 (38.5)	13 (31.7)
Biochemical parameters, mean±SD		
AST (IU/l)	**142.7±40.7**	**106.8±52.3***
ALT (IU/l)	**180.5±52.0**	**139.5±57.3***
AF (IU/l)	72.1±16.7	64.4±18.1
AFP (ng/ml)	4.7±2.1	3.5±3.3
Bilirubin unconjugated (μmol/l)	12.3±4.2	10.4±3.9
Bilirubin conjugated (μmol/l)	3.3±1.7	2.5±1.2
Blood Proteins (g/l)	73.2±3.9	73.0±6.2
Albumins (g/l)	45.7±4.2	45.7±3.8
Globulins (g/l)	28.3±6.3	27.3±7.1
INR (s)	1.0±.1	1.0±0.1
Triglycerides (mmol/l)	1.5±0.8	1.3±0.6
Cholesterol (mmol /l)	4.0±1.5	4.3±1.0
Laboratory data, median (range)		
RBC baseline (x10^{12} cells/L)	4.19 (2.69-4.68)	4.36 (3.11-5.52)
RBC EOT (x10^{12} cells/L)	3.57 (2.15-4.64)	3.72 (2.66-4.66)
Hgb baseline (g/L)	136 (102-168)	132 (96-164)
Hgb EOT (g/L)	104 (76-142)	115 (84-139)
Platelet baseline (x10^9 cells/L)	142 (54-324)	142 (59-311)
Platelet EOT (x10^9 cells/L)	**136 (59-248)**	**110 (39-174)***
WBC baseline (x10^9 cells/L)	4.32 (2.30-6.05)	5.18 (2.88-8.50)
WBC EOT (x10^9 cells/L)	**5.04 (2.16-8.93)**	**3.65 1.93-5.62)***
Neutrophil baseline (x10^9 cells/L)	2.06 (0.86-3.02)	2.02 (0.86-3.17)
Neutrophil EOT (x10^9 cells/L)	**1.85 (1.01-2.45)**	**1.49 (0.72-2.59)***

We compared all of the data between the patients with and without sustained virological response. As shown in Table 2, there was no statistically significant difference between groups in relation to gender, age, basal viral load, virus genotype, infection route or fibrosis stage. Among the biochemical parameters tested, only AST and ALT serum levels were significantly higher in patients with poor response to therapy (p<0,05). For haematological parameters, RBC count and haemoglobin levels decreased in both groups during treatment, but there was no significant difference between the two groups at the end of therapy (Figure 2). Platelet and white blood cell counts were within

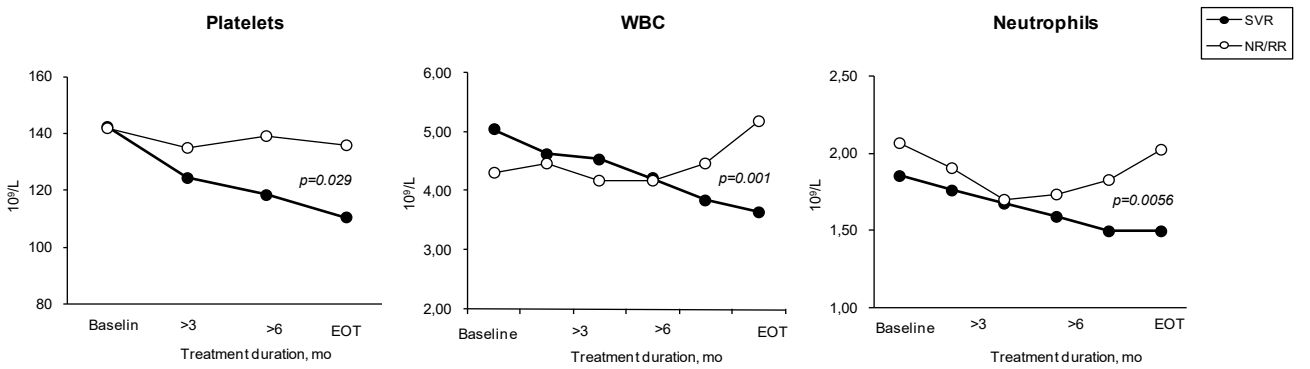

Figure 3. Median platelet, WBC and neutrophil counts in SVR and NR/RR groups before treatment (baseline), 3 and 6 months after beginning treatment and at the end of therapy (EOT); *Differences between SVR and NR EOT time points were determined using a Mann-Whitney U-test.*Differences between SVR and NR EOT time points were determined using a Mann-Whitney U-test.

the normal range in NR/RR patients during therapy, but decreased in the SVR group. At the end of therapy, there was a statistically significant difference in these values between the two groups (Pt: p<0,05 and WBC: p<0,001). The neutrophil count decreased during the first 3 months of treatment in both groups. Neutrophil counts continued to decrease in the SVR group, but increased back to baseline in the NR/RR group. The neutrophil count at the end of treatment was statistically lower in responders than in patients with poor response (p=0,005) (Figure 3).

To identify clinically relevant associations between the analysed parameters and the treatment outcome, we determined independent predictors for sustained virological response using logistic regression and multivariate analysis. Of the parameters analysed in the univariate model, we found a negative association between therapy response and platelet, WBC and neutrophil counts. The results showed that therapeutic response depends on platelet count (Odds ratio=0.869; 95% CI=0.772–0.979; p=0.020), as an increase in platelet count reduces the chances for a good therapeutic response by 13.1%. Similarly, treatment response depends on WBC (Odds ratio=0.018; 95% CI=0.001–0.0.396; p=0.011) and neutrophil counts (Odds ratio=0.003; 95% CI=0.000–0.182; p=0.006) such that an increase in WBC or neutrophil count reduces the chances for a good therapeutic response by 82% and 97%, respectively. However, the multivariate model showed that the most significant predictors of treatment response were WBC (Odds ratio=0.013; 95% CI=0.000–0.656; p=0.030) and neutrophil count (Odds ratio=0.000; 95% CI=0.000–0.273; *p*=0.018).

DISCUSSION

Considering the insufficient efficacy (55-60%), cost and diverse side effects of PEG-IFNα-2a+RBV therapy (7, 9) it is important to determine the factors that influence or are associated with response. The major predictors for achieving sustained virological response were viral genotype and basal viral load. HCV genotype 1 infection and viral load >600.000 IU/ml are related to poor therapy response (10, 11). Among other factors, male sex, age >40 years and advanced fibrosis have been shown to predict a lower response rate (12, 13). However, in our study, gender, age, basal viral load, HCV genotype, histopathology and risk factors for acquiring HCV infection were not associated with therapy response (p>0,05). These discrepancies may be related to the size of the study group, as our previously published data with a larger group of 121 patients showed that treatment outcome was associated with baseline HCV RNA, HCV genotype, infection route and the degree of histopathological liver changes (14).

Clinical data regarding the relevance of transaminase levels and therapy outcome are conflicting. While Zeuzem et al. showed that patients with elevated transaminases respond better to therapy (15), Gordon et al. found that reaching SVR is independent of the ALT baseline level (16). Our results are inconsistent with those findings, as we found that patients with a poor response to therapy had significantly higher baseline AST and ALT levels (p<0,05).

Common side effects of PEG-IFNα-2a+RBV therapy include anaemia, leucopoenia and thrombocytopenia (17-19). Ribavirin has haemolytic effects and often causes anaemia, whereas IFNα has been shown to suppress haematopoietic progenitor cells in the bone marrow to induce leucopoenia and thrombocytopenia (20-22). Likewise, our study showed a statistically significant decrease in Hgb levels and RBC, Pt, WBC and Ne counts (p<0,001).

Recent studies have shown that the degree of haemoglobin alleviation during therapy is associated with a higher response rate (23, 24). We did not observe such a relationship, but found a similar decrease in Hgb levels and RBC counts in both the SVR and the NR/RR groups. However, the Pt, WBC and Ne counts decreased in the SVR group, and they were significantly lower at the end of treatment in the SVR group compared with the NR/RR group. Our results are consistent with previous findings that leucopoenia and thrombocytopenia are significantly more pronounced in patients who achieved sustained virological response (8, 25). We suggest that this difference is related to individual variations in pharmacokinetics and biochemical and physiological effects of drugs.

In conclusion, our study showed that treatment failure was significantly associated with higher baseline AST and ALT levels. All treated patients developed anaemia, irrespective of therapy response. Sustained virological response occurred more often in patients who developed thrombocytopenia, leucopoenia and neutropenia.

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