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POSSIBLE DIFFERENCES IN HEMATOLOGICAL ADVERSE EFFECTS IN MALES AND FEMALES DURING CHRONIC HEPATITIS C INFECTION THERAPY

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Chronic HCV infection therapy with pegylated-interferon plus ribavirin is associated with many adverse effects. The aim of our study was to determine the incidence of hematological adverse effects and their possible differences in males and females during chronic HCV infection therapy, as well their influence on the therapy course and duration.

The study involved 55 patients divided into four groups. Group I comprised male patients treated for 48 weeks (24 patients); group II - females treated for 48 weeks (14 patients); group III - males treated for 24 weeks (14 patients) and group IV - females treated for 24 weeks (3 patients). The following hematological parameters were examined: leukocyte, neutrophil, erythrocyte and thrombocyte count, hemoglobin concentration and hematocrit.

Ninety-two percent of patients had hematological adverse effects in total. Anemia was registered in 35 patients: in 71% of males in group I, 86% of females in group II, and in group III in 43% of cases. There is no statistically significant difference in the incidence of anemia between groups I and II patients, but it is relevantly more frequent in group II compared to group III, with the shorter duration of treatment ($p<0.05$). Additionally, significantly lower average hemoglobin concentration decrease was reported in subjects of group III ($p<0.01$). Leucopenia, neutropenia and thrombocytopenia were noticed in approximately the same number of males and females, while one male in group I suffered from severe thrombocytopenia. Nineteen patients had to have medications dose modification due to these side effects.

According to our research, females suffered from anemia more frequently, while the frequency of other cytopenias was almost equal between genders. The medications dose modifications due to these side effects did not influence the therapy course and duration. It is important to note that the patients with 24-week-therapy had less hematological side effects compared to the patients treated for 48 weeks. The indicated differences reveal the need for possible corrections in therapeutic approach according to patient gender in order to achieve effective disease management with less adverse effects. *Acta Medica Medianae 2010;49(2):.9-14.*

Key words: *chronic hepatitis c, adverse effects, male, female*

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Introduction

Hepatitis C viral (HCV) infection represents a worldwide health problem. It is believed that 2–3% of the world population is persistently infected, or 180 million people (1-4). HCV infection manifests in 15% as acute viral hepatitis, in 60 to 70% as chronic hepatitis and up to 50% as cirrhosis, end-stage liver disease or liver cancer (1,2,5). Up to 20% of patients with chronic HCV infection progress to cirrhosis after an average of 20 years, and 5% will develop hepatocellular carcinoma (4,5).

Hepatitis C virus is a single-stranded RNA virus, with six known genotypes and more than 50 subtypes (5). It is spread primarily by a contact with infected blood and blood products. These patients mostly have in their anamnesis data of injection-drug abuse or a contact with blood products (1,6,7).

Introduction of pegylated interferon alfa-2a (PEG-IFN) and ribavirin, as the standard therapy for chronic HCV infection, has brought to the significant progress in healing of these patients. Undetectable HCV-RNA in the serum six months after completing the therapy is considered as a sustained virological response (SVR) (2,4,8). Patients infected with virus genotypes 2 and 3 are treated for 24 weeks, which mostly results in SVR in 80%. While patients with virus genotypes 1, 4, 5 and 6 need higher doses of ribavirin in addition to PEG-IFN for 48 weeks; the estimated SVR is 50% (5,8).

PEG-IFN and ribavirin therapy is associated with high incidence of side effects, therefore, sometimes it is necessary to reduce the doses of these drugs (8,9). Hematological side effects are common: bone marrow suppression induced by interferon may result in neutropenia and thrombocytopenia, while ribavirin causes a direct hemolysis of erythrocytes (2,5,8). Other side effects include:

flu-like syndrome, CNS disorders, cardiovascular, gastrointestinal, endocrine, kidney damage and other (2,5,7).

The normal physiological and psychological gender variations can sometimes be the cause of the health differences. Males and females may have different symptoms of HCV infection as well as side effects and success of the therapy. In general, however, the therapy side effects are the same for male and female patients (10-12).

Aims

The aim of our study was to determine the incidence of hematological side effects and their possible differences in males and females with chronic HCV infection during the pegylated interferon alfa-2a and ribavirin therapy, as well their influence on the therapy course and duration.

Patients and methods

During this prospective-retrospective study, 65 patients with chronic HCV infection were examined at the Clinic for Infectious Diseases in Niš, between 2006 and 2009. Chronic HCV infection was diagnosed with ultrasound, biochemical and serological tests (anti-HCV antibody) and confirmed using polymerase chain reaction (PCR) assay (Amplicor Monitor Assay; Roche Molecular Systems) at the Institute for Infectious and Tropical Diseases in Belgrade.

Chronic hepatitis C infection treatment was carried out using the combination therapy: Pegasys (Pegylated interferon alfa-2a; Hoffmann-La Roche Inc.) and Copegus (Ribavirin; Hoffmann-La Roche Inc.). Patients with virus genotypes 1 and 4 received PEG-IFN for 48 weeks at 180 μg once a week by subcutaneous injection and ribavirin at 1000-1200 mg/day per os; patients with virus genotypes 2 and 3 received PEG-IFN for 24 weeks at 180 μg once a week and ribavirin at 800–1000 mg/day. Ten patients with acute HCV infection, chronic renal diseases on dialysis or previous cytopenia were excluded from the study.

All patients were followed up clinically and biochemically every 15 days. We divided the therapy adverse effects in hematological and non-hematological, and then examined the following hematological parameters: leucocytes (WBC), neutrophils (NE), erythrocytes (RBC), hemoglobin (HGB), hematocrit (HCT) and thrombo-cytes (PLT).

The dose of PEG-IFN was reduced from 180 μg to 135 μg or 90 μg for every neutrophil count drop of 250 cells/mm3, while the ribavirin dose was reduced to 600mg/day if HGB level was <100g/L, similarly to other authors' procedures (9,13).

Fifty-five patients were divided into four groups and analyzed: group I comprised male sex subjects with virus genotypes 1 and 4 (24 patients), group II females with genotypes 1 and 4 (14 patients), group III males with virus genotypes 2 and 3 (14 patients), and group IV females with genotypes 2 and 3 (3 patients). Two patients had mixed infection. Group IV was excluded from the study because of the small number of subjects and then we continued to compare with groups I, II and III, or 52 patients.

Pathohistological (PH) examination of liver was performed before the therapy started, except in patients with hemophilia and von Willebrand disease (8 patients). Liver fibrosis levels were classified on a scale of F0-F4 according to the Metavir scoring system (14). Efficacy of the therapy was evaluated at the end of the treatment (ETR), after 24 and 48 weeks using the PCR assay. ETR is defined as undetectable HCV-RNA in the serum at the end of the treatment (15,16).

Results are expressed as the average value ± standard deviation (SD). Statistical signifi-cance was tested using the Student's t-test and Pearson correlation coefficient; probability value (p) lower than 0.05 was considered statistically significant. Data analysis was performed using Microsoft Office Excel 2003 program package in Windows XP Profe-ssional environment.

Results

Out of 52 examined subjects, with average age of 41±15 years, 38 were male (73%) and 14 were of female sex (27%). Virus genotype 1 was the most frequent among them (69%), while ways of infection remained unknown in half of the patients. The patients mostly had liver fibrosis level F2 (28.8%) and viral HCV-RNA load in the serum less than 1 million copies IU/ml (34.6%). Details of these patients' characteristics are shown in Table 1.

Seventy-six percents of patients achieved a complete response, but without significant difference according to their gender. The therapy adverse effects were present in a significant number of the patients (92%). Even 92% had a decrease in some of the monitored hematological parameters compared to the values at the beginning of the treatment: all females (all parameters, $p<0.01$), 92% of males in group I (all parameters, $p<0.01$; PLT, $p<0.05$) and 86% of group III males (WBC, $p<0.05$; RBC, HGB and HCT, $p<0.01$).

Cytopenia was present in 86.5% of patients in: 83%, 100% and 78.6%, respectively. Anemia was registered in 35 patients (67.3%), leucopenia and neutropenia in 31 patients (59.6%) and thrombo-cytopenia in 13 patients (25%). Comparison of cyto-penias in patients by the group is shown in Figure 1.

Significantly lower values at the end of the treatment of RBC ($p<0.05$), HGB and HCT ($p<0.01$) were reported in females compared to males from both groups. However, most of them had lower values of these parameters ($p<0.05$) before starting the treatment. Although a larger number of females had anemia (86%), no significant difference was found compared to the males from group I (71%), only in relation to the males from group III (43%, $p<0.05$). At the same time, significantly more females had hematocrit decrease than males in both groups ($p<0.05$). The average values of hemato-logical parameters decrease are shown in Table 2.

There was a significant correlation between the female patients' age and the HGB level decrease ($r=0.5$, $p<0.01$), while a significant negative correla-tion was determined between the HGB levels at the beginning and the end of the therapy in all patient

groups (r=0.5, r=0.6, r=0.87, p<0.01).

Also, 70% of patients had some non-hematological side effects reported. Two patients suffered severe side effects and had to discontinue their therapy for a week (3.8%): pneumonia (female) and severe thrombocytopenia with hemorrhagic syndrome (PLT<30x1012/L) (group I male).

PEG-IFN and ribavirin dose modification had 36.5% of patients for 1 or 2 weeks, by the groups: 37.5%, 57% and 14%, respectively. One male patient of group I had the ribavirin dose reduced while other modifications were related to PEG-IFN. Therapeutic protocols were fulfilled completely in all patients.

Table 1. Patients with HCV infection characteristics

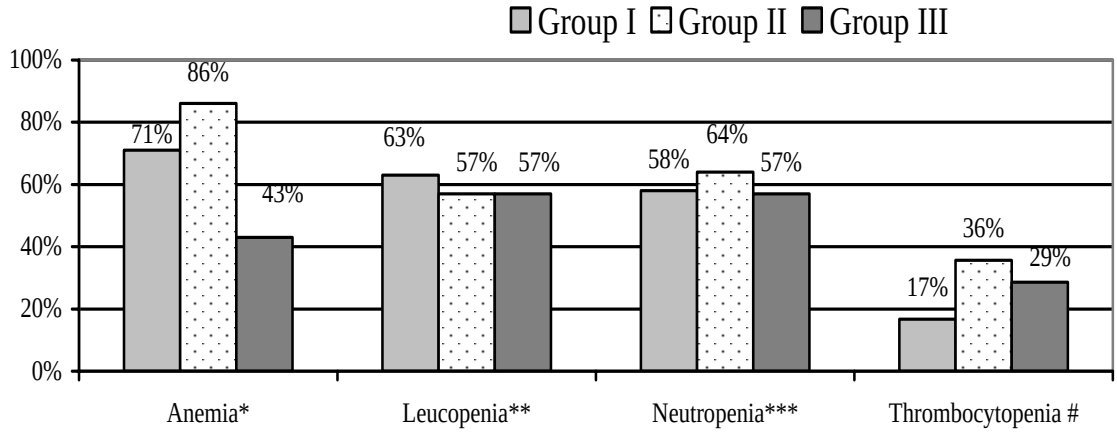
	Group I		Group II		Group III	
Virus genotype	N	%	N	N	%	N
Genotype 1	23	95.8	13	93	/	/
Genotype 2	/	/	/	/	1	7
Genotype 3	/	/	/	/	13	93
Genotype 4	/	/	/	/	/	/
Mixed infection	1	4.2	1	7	/	/
Liver PH finding	N	%	N	%	N	%
F0	0	0	3	21.4	0	0
F1	8	33.3	2	14.3	4	28.6
F2	7	29.2	2	14.3	6	42.8
F3	1	4.2	1	7	1	7
F4	3	12.5	5	35.7	1	7
Without PH	5	20.8	1*	7	2	14.3
Means of infection	N	%	N	%	N	%
Unknown	11	45.8	11	78.6	4	28.6
Drug abuse	8	33.3	2	14.3	9	64.3
Transfusion	5	20.8	1	7	1	7
Number of viral copies in the serum	N	%	N	%	N	%
< 1 million/ml	10	41.7	5	35.7	3	21.4
1 to 5 million/ml	7	29.2	7	50	3	21.4
5 to 10 million/ml	1	4.2	2	14.3	3	21.4
> 10 million/ml	6	25	0	0	5	35.7

* von Willebrand disease

Table 2. Average values of hematological parameters' decrease

	WBC ($x10^9$/L)	NE ($x10^9$/L)	RBC ($x10^{12}$/L)	HGB (g/L)	HCT (%)	PLT ($x10^9$/L)
Group I	0.67	0.48	0.52	22.8	4.98	33.4
Group II	1.2	0.77	0.66	24	4.87	67.4
Group III	1.6	1.30	0.47	5.25*	3.63	27.7

* lower value decrease compared to group I and II, p<0.01



* RBC< 4x1012/L for females and <4.2x1012/L for males and/or HGB <120g/L for females and <130g/L for males and/or HCT<36% for females and <39% for males;
** WBC< 4x109/L;
*** NE <2.1x109/L;
# PLT< 100x109/L

Figure 1. Cytopenia ratio by patient groups

Discussion

The prevalence of HCV infection is higher among men than women, which is also present in our study, as nearly three times more men had the infection (73% vs. 27%). Men are probably more exposed to risk factors for HCV infection, such as higher prevalence of injection-drug abuse among them, because susceptibility for the virus is the same among genders (6,12). This is partly because men suffer from hemophilia more frequently and were receiving clotting factors treatment before 1987, when no HCV blood testing existed (17).

Women are less likely to progress from acute to chronic disease as well to have complications, as women have 5% likelihood of progressing to cirrhosis, compared to 20-30% likelihood in men. At the same time, men are 4 times more likely to develop liver cancer due to HCV (11-13). In our study, there were no significant differences in pathohistological findings of the liver according to gender.

Still unexplained higher rate of spontaneous HCV clearance is more frequently seen in females (10-12). It is known that early and strong CD4+/Th1 immune response against HCV plays an important role in these patients resolution (18). According to some researches, these differences are present due to the female sex hormone estrogen, which protects liver from damage. However, its protective effect may diminish after menopause. In this context, older women are more likely to have more liver damage and lower response rates to the therapy. Despite, an older age is not an unfavorable marker for the therapy application (11,19,20).

Also, females are reported to have slightly higher complete therapeutic response rates and are cured in a greater percentage, but till now no relationship was determined between genders and therapy success (10-12,19). We have not found significant difference among genders in respect to therapy response.

Pegylated interferon plus ribavirin therapy has a fundamental role in healing patients with chronic hepatitis C virus infection today. Some authors indicate that the therapy is better tolerated for 24 than 48 weeks, and that the incidence of adverse effects, dose reductions and therapy withdrawals is distinctly lower in patients with shorter duration of the therapy (3,21). In our case, males from the group III, treated for 24 weeks, had anemia 1.5 and 2 times less frequently than patients treated for 48 weeks. Even though they also had decrease in hematological parameters, no significant difference was found in relation to the males treated for 48 weeks. However, males from the group III had significantly lower fall of monitored parameters and had anemia less than the females (86% vs. 43%, $p<0.05$). Although the therapy side effects are considered to be the same for males and females in general, certain studies report that female experience side effects more frequently, but milder and with later development (10,11).

Cytopenias are the most common complications of this therapy as even 92% of our patients had decrease in some monitored hematological parameter. Anemia is likely due to the combination of ribavirin-induced erythrocyte hemolysis and hematopoietic suppression of bone marrow by interferon (22). Ribavirin is concentrated into red blood cells, which causes oxidative cell injury, decreases activity of erythrocyte Na+-K pump and increases reticulocytosis and sequestration of erythrocytes by the mononuclear phagocyte system, thereby shortens theirs survival (5,7,8). Compensatory reticulocytosis is lesser in these patients, suggesting that interferon bone marrow suppression prevents an adequate reticulocytosis. This process is generally slower and may affect the continued decline in hemoglobin concentration during the treatment (8,22).

Females had significantly lower values of RBC ($p<0.05$), HGB and HCT ($p<0.01$) at the end of treatment. In addition, more females had anemia than males from group I (86% vs. 71%), but no statistically substantial difference was found between them. Significant difference was present in relation to the male patients treated for 24 weeks ($p<0.05$). Similar studies have also found that females are more likely to develop anemia. It is known that they naturally have less hemoglobin and so a higher risk to develop anemia, especially menstruating women (11,22,23).

The degree of cytopenias in our patients was mostly mild to moderate in severity with the mean hemoglobin level decrease of 22.1 g/L in females and 17.7 g/L in group I males. The hematocrit decrease was 6.3% and 5.5%, respectively, similarly to other studies (5,6). None of our patients had a hemoglobin level decrease less than 85g/L, which is considered to be the limit for severe anemia and which some authors find more often in females. Also, it is reported that males may experience greater reduction in serum hemoglobin during the therapy, which was not the case in our study (23).

According to literature, older age, cirrhosis, impaired renal function, higher HGB levels at baseline, female sex and ribavirin dose are the factors associated with relevant decrease in HGB and development of anemia (5,13,22). We determined a significant positive correlation between females' age and greater fall of HGB concentrations ($r=0.5$, $p<0.01$), which might mean that older females are more likely to acquire anemia during this therapy. Besides, significant negative correlation between higher HGB levels at baseline and their fall during the treatment was determined in all patients.

In clinical practice, standard management of interferon and ribavirin hematological side effects is dose reduction (8,9,13). Nineteen of our patients (36.5%) had the medication dose modification, lasting one or two weeks. Only one group I male patient with severe thrombocytopenia had to have ribavirin dose reduction, while other modifications were related to PEG-IFN.

It is important to early reduce the dose of ribavirin in patients with marked fall in HGB, in order to continue the therapy safely, while discontinuation of ribavirin intake is recommended if severe anemia occurs (HGB< 85g/L or HCT

< 26%) (5,21). It is also preferable to maintain optimal or nearly optimal doses of PEG-IFN and ribavirin as long as possible. The currently recommended goal is to maintain at least 80% of the medications' doses for at least 80% of the treatment duration, as patients who succeed in this have better chances in achieving SVR (24,25). Because of the clear relationship between ribavirin concentrations and SVR rate, it is preferable not to reduce its dose if possible. Accordingly, gradual ribavirin dose reduction regimens (by 200 mg at a time) may be more appropriate in preventing anemia, while maintaining a high probability of achieving SVR (5,13,25).

The cause of neutropenia and thrombocytopenia is usually interferon-induced bone marrow suppression. Neutropenia may develop a risk for infections, especially at neutrophil count lower than 500 cells/mm^3. According to some authors thrombocytopenia is rarely clinically manifested and only 5% of patients require medications dose reduction. The therapy discontinuation is recommended when thrombocyte count falls below $30x10^9$/L. Neutrophil and thrombocyte count as well as hemoglobin level rapidly return to baseline after the therapy is discontinued (8,10,22,26).

In our study, approximately the same number of females and males had leucopenia, neutropenia and thrombocytopenia, and there was no significant difference between these hematological parameters. Patient from group I with severe thrombocytopenia had to discontinue his therapy for a week. Severe type of neutropenia or thrombocytopenia is a very rare side effect, it is present in less than 2% of patients (5). The PEG-IFN dose reduction is necessary when the neutrophils level falls under 750 cells/mm^3, while PEG-IFN administration must be stopped if a neutrophil count is less than 250 cells/mm^3 (5,26). Eighteen of our patients had PEG-IFN dose modifications. However, the medication dose modifications and therapy discontinuations did not affect the expected ETR rate in our patients.

Conclusion

During the pegylated interferon and ribavirin therapy, female sex had anemia in a larger number. The susceptibility to anemia may be increased due to usually lower values of anemia parameters in females.

The incidence of leucopenia, neutropenia and thrombocytopenia was the same among genders.

The medication doses were modified in nineteen patients but did not affect the overall duration of the treatment and expected ETR rate.

The male group treated for 24 weeks had less hematological adverse effects.

The problems described in our study reveal the need for a maybe different approach to the patient treatment with regard to gender.

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MOGUĆE RAZLIKE U HEMATOLOŠKIM NUSEFEKTIMA KOD MUŠKARACA I ŽENA TOKOM TERAPIJE HRONIČNOG HEPATITISA C

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Terapija hronične hepatitis C infekcije pegilovanim-interferonom i ribavirinom je praćena brojnim nusefektima. Cilj našeg istraživanja bio je utvrđivanje učestalosti hematoloških nusefekata i njihovih eventualnih razlika kod muškaraca i žena tokom terapije hronične HCV infekcije, kao i njihov uticaj na terapijski tok i trajanje.

Istraživanjem je obuhvaćeno 55 bolesnika podeljenih u četiri grupe. Grupu I su činili bolesnici muškog pola lečeni 48 nedelja (24 bolesnika); grupu II žene lečene 48 nedelja (14 bolesnica), grupu III muškarci lečeni 24 nedelje (14 bolesnika) i grupu IV žene lečene 24 nedelje (3 bolesnice). Ispitivani su sledeći hematološki parametri: broj leukocita, neutrofila, eritrocita, trombocita, koncentracija hemoglobina i hematokrit.

Ukupno 92% bolesnika imalo je hematološke nusefekte. Anemija je registrovana kod 35 bolesnika: u grupi I kod 71% muškaraca, u grupi II kod 86% žena i u grupi III kod 43% ispitanika. Ne postoji statistički značajna razlika u učestalosti anemije kod bolesnika I i II grupe, ali je ona značajno češća u grupi II u odnosu na grupu III, sa kraćim trajanjem terapije ($p<0.05$). Ujedno, značajno manji prosečni pad koncentracije hemoglobina imali su ispitanici grupe III ($p<0.01$). Kod približno istog broja muškaraca i žena primećena je leukopenija, neutropenija i trombocitopenija, dok je tešku trombocitopeniju doživeo jedan muškarac grupe I. Devetnaest bolesnika je zbog ovih nusefekata imalo modifikaciju doze lekova.

Prema našem istraživanju, žene su nešto češće imale anemiju, dok je učestalost ostalih citopenija bila skoro jednaka u oba pola. Modifikacije doze lekova usled ovih nusefekata nisu uticale na tok i trajanje terapije. Bitno je napomenuti da su bolesnici sa kraćim trajanjem terapije od 24 nedelje imali manje hematoloških nusefekata u odnosu na bolesnike sa 48 nedelja terapije. Navedene razlike otkrivaju potrebu eventualne korekcije terapijskog pristupa u zavisnosti od pola radi efikasnijeg savladavanja bolesti sa manje nusefekata. *Acta Medica Medianae 2010;49(2):9-14.*

***Ključne reči**: hronični hepatitis C, neželjeni efekti, muškarci, žene*