Published online:01/04/2016 Published print:04/2016

ORIGINAL PAPER

doi: 10.5455/medarh.2016.70.127-130
Med Arch. 2016 Apr; 70(2): 127-130
Received: FEB 25, 2016 | Accepted: MAR 25, 2016

The Effect of Combination Antiviral Therapy in the Treatment of Hepatitis C on the Occurrence of Depressive Disorder in Patients Treated for Hepatitis C in the Republic of Srpska

Visnja Banjac, Nera Zivlak-Radulovic, and Mirjana Miskovic

Clinic of Psychiatry, University Clinical Center Banja Luka, Banja Luka, B&H

Corresponding author: Visnja Banjac, MD. Clinic of Psychiatry, University Clinical Center of the Republic of Srpska. Macvanska 17, 78000 Banjaluka, Bosnia and Herzegovina. + 387 65 462 496 E-mail: visnjab76@hotmail.com

ABSTRACT

Background. The current standard treatment of chronic hepatitis C in Bosnia and Herzegovina consists of pegylated interferon alpha in combination with ribavirin. Interferon therapy has many psychiatric side effects, with depressive symptomatology being most prominent. The aim of the study was to establish the frequency and severity of depression in patients with chronic hepatitis C during two months of the aforementioned therapy. **Subjects and Methods.** The overall sample consisted of 46 subjects, divided into three subgroups, aged 18 to 65. The study population consisted of subjects treated for chronic hepatitis C (n = 15), subjects infected but not treated for chronic hepatitis C (n = 15), and healthy controls (n = 16). The assessment and level of depression were based on the Structural clinical interview (SCID), Montgomery-Asberg Depression Rating Scale and Zung Self-Rating Depression Scale. The assessments were conducted before interferon therapy (on the day 0), after 4 and 8 weeks of therapy. **Results.** Regarding its frequency, MADRS scoring showed that the number of depressed subjects receiving therapy increased after 8 weeks (46.7%). There was statistical significance between the subgroups after 4 and 8 weeks. Likewise, the ZUNG scale showed that the number of depressed subjects receiving therapy increased after 8 weeks (73.3%). There was statistical significance between the subgroups on the day 0, after 4 and 8 weeks. **Conclusions.** Depression was significantly more frequent in chronic hepatitis C subjects treated with interferon alpha in combination with ribavirin than in subjects in the group without therapy. Mild depression was most prevalent.

Key words: **chronic hepatitis C, pegylated interferon, depression, assessment instruments, correlation.**

1. INTRODUCTION

Chronic hepatitis C is a chronic disease and whose global prevalence is estimated at 3% of the world's population (1). According to the Word Health Organization, the assumed prevalence of chronic hepatitis C in Bosnia and Herzegovina is around 1.5%. The current standard treatment of chronic hepatitis C in Bosnia and Herzegovina consists of the use of pegylated interferon alpha, subcutaneously, once a week, combination with ribavirin, daily (PEG-INF-α-2a+RBV). The treatment lasts between 48 or 24 weeks (2). Interferon therapy is associated with many psychiatric significant adverse effects (insomnia, tension, irritability, dispersion, forgetfulness), and the most prominent form is depressive symptomatology (3, 4). In 30-50% of cases depression is the most common adverse effect of interferon therapy and it can compromise the effect of treatment (5). Since this kind of

study has never been conducted in Bosnia and Herzegovina before, the aim was to provide a better screening of a group of patients with a high risk of manifestation of depressive symptoms during interferon therapy. The study would help identify the risk factors for the development of depression and enable prevention of deepening of depressive symptoms.

2. MATERIAL AND METHODS

The research was designed as a prospective clinical study. The study population consisted of 46 subjects, 15 subjects treated for hepatitis C with combination therapy, 15 subjects diagnosed but not treated for hepatitis C with combination therapy and 16 healthy controls, aged 18 to 65 years, gender equated, different educational background, with different stages of the disease. Prior to the study, the subjects had to sign a consent form in accordance with the previous authorization by the Ethics Committee. The eligibility criteria were as follows: subjects with a certified clinical and diagnosed chronic hepatitis C. The exclusion criteria were as follows: other liver diseases, abuse of psychoactive substances in the previous six months, attempted suicide in the history, subjects with psychiatric disorders such as psychosis from the schizophrenic specter, mood disorders, delusional disorders, dementia and other serious organic brain disorders, subjects with neurological diseases such as epilepsy, Parkinson's disease, cardiovascular diseases (decompensated heart failure), coinfection with hepatitis B or HIV, autoimmune disorders, unregulated diabetes, number of neutrophils under 1,500/cm^3 and number of thrombocytes under 75,000/cm^3.

The assessment and level of depression were based on the Structural clinical interview (SCID), Montgomery-Asberg Depression Rating Scale and Zung Self-Rating Depression Scale.. This study was carried out during a period of two months. The assessments were conducted before interferon therapy (on the day 0), after 4 and 8 weeks of therapy.

The methods of descriptive and analytic statistics were used for statistical processing of data. The differences between the subjects and other characteristics were assessed using the following tests: a) parametric tests (Student's t-test, one-way analysis of variance - ANOVA and Pearson's Chi-Square test) and b) nonparametric tests (Chi-Square Test of homogeneity, Mann Whitney U test, Kruskal-Wallis test, Wilcoxon singed-rank test and Friedman two-way analysis of variance by ranks). The strength of the connection between the characteristics of observation was assessed using Spearman's rank correlation coefficient. Models of logistic regression were used to predict the value of observed characteristics. SPSS software system version 20 was deployed in processing statistical data.

3. RESULTS

Socio-demographic characteristics of the subjects are presented in Table 1 (gender, age, marital status, education, employment, presence of psychiatric disorders in the history). There were more male subjects (66.7%) in the PEG-INF-α-2a+RBV subgroup, and (93.3%) in the no treatment subgroup, and least in the healthy subgroup (6.2%). There was statistical significance on gender match between the groups (treatment, no treatment, healthy controls), (p= 0,000 <0,05).

The mean age was 41.07 years. There was statistical significance between the subgroups on age match (treatment, no treatment, healthy controls). The mean age was 43.47, 32.27 and 47.06 years (p= 0,000 <0,05), respectively. The majority of the subjects were unemployed (54.3%). There was statistical significance between the tested groups on employment match (p= 0,000 <0,05).

Subjects with high school education prevailed in the treatment and no treatment subgroups, while the healthy controls were mostly college/university graduates. There was statistical significance between the subgroups on education match (p=0,000 <0,05).

Majority of the subjects in the treatment subgroup were married (60%), the healthy subgroup (75%) respectively, while in the no treatment subgroup singles prevailed. There was no statistical significance between the tested groups on marital status match (p=0,140 >0,05).

In the treatment subgroup 46.7% of the subjects had some sort of psychiatric disorder in the history, and 53.3% in the no treatment subgroup, respectively. There was statistical significance between the subgroups (p=0,002 <0,05).

MADRS scoring showed that the number of depressed subjects in the treatment subgroup increased after 8 weeks (46.7%), and a rise after 4 and a decrease after 8 weeks in the no treatment subgroup, respectively. There was statistical significance between the subgroups after 4 and 8 weeks (Table 2). The findings further showed the presence of mild depressive symptomatology in the subgroups, while severe depression was not recorded. There was no statistical significance between the subgroups on depression degree match at any week.

Basic characteristics	Number of (%) subjects			Total (n=46)	p
	with PEG-IFN-α-2a+RBV	without PEG-IFN-α-2a+RBV	healthy controls		
Gender male female	 10 (66.7) 5 (33.3)	 14 (93.3) 1 (6.7)	 1 (6.3) 15 (93.8)	 25 (54.3) 21 (45.7)	p=0,000
Mean age ±SD	43.47±11.11	32.27±4.99	47.06±8.76	41.07±10.59	p=0,000
Marital status Married Rest (single, divorced, widowed)	 9 (60) 6 (40)	 6 (40) 9 (60)	 12 (75) 4 (25)	 27 (58.7) 19 (41.3)	p=0,140
Education Elementary school High school College/ University	 1 (6.7) 10 (66.7) 4 (26.6)	 0 (0) 15 (100) 0 (0)	 0 (0) 3 (18.8) 13 (81.2)	 1 (2) 28 (61) 17 (37)	p=0,000
Employment Unemployed Employed	 11 (73.3) 4 (26.7)	 13 (86.7) 2 (13.3)	 1 (6.2) 15 (93.8)	 25 (54.3) 21 (45.7)	p=0,000
Psychiatric disorders in the anamnesis yes no	 7 (46.7) 8 (53.3)	 8 (53.3) 7 (46.7)	 0 (0) 16 (100)	 15 (32.6) 31 (67.4)	p=0,002

Table 1. Socio-demographic characteristics of the subjects

Week	Group	Number of depressed subjects (percentage %)	p
0	with PEG-IFN-α-2a+RBV without PEG-IFN-α-2a+RBV healthy controls	40 26.7 0	P= 0,022 < 0,05
4	with PEG-IFN-α-2a+RBV without PEG-IFN-α-2a+RBV healthy controls	66.7 40 0	P=0,000 < 0,05
8	with PEG-IFN-α-2a+RBV without PEG-IFN-α-2a+RBV healthy controls	73.3 26.7 0	P=0,000 < 0,05

Table 3. Frequency of depression across the subgroups (Zung Scale)

Week	Subgroup	Number of depressed subjects (percentage %)	p
0	with PEG-IFN-α-2a+RBV without PEG-IFN-α-2a+RBV healthy controls	13.3* 13.3 0	P=0,311 >0,05
4	with PEG-IFN-α-2a+RBV without PEG-IFN-α-2a+RB healthy controls	40 20 0	P=0, 020 <0,05
8	with PEG-IFN-α-2a+RBV without PEG-IFN-α-2a+RBV healthy controls	46.7 13.3 0	P=0,004 <0,05

Table 2. Frequency of depression across the subgroups (MADRS Scale)

	ZUNG (weeks)		
MADRS weeks	0	4	8
0 correlation coefficient	0,736	0,789	0,751
P	0,000	0,000	0,000
4 correlation coefficient	0,660	0,756	0,747
P	0,000	0,000	0,000
8 correlation coefficient	0,646	0,734	0,781
P	0,000	0,000	0,000

Table 4. Connection between depression assessment instruments – MADRS and Zun *Spearman's rank correlation coefficient

The findings showed a rise in the number of depressed subjects in the treatment subgroup after 8 weeks (73.3%), and a rise after 4 and a decrease after 8 weeks in the no treatment subgroup, respectively. There was statistical significance between the subgroups on the day 0, after 4 and 8 weeks (Table 3). The findings showed that depression in remission was present most across the subgroups, while severe depression (hospitalization) was less present. There was statistical significance between the subgroups on depression degree match.

Assessment of the significance of individual factors on the occurrence of depression was based on the binary logistic regression model. This model was used for gender, age, marital status, education, employment, psychiatric disorder in the history match. Logistic regression model indicated statistical significance $\chi 2(8)=20040$, $p=0.010<0.05$. The model showed 54% of variance in the dependent variable (occurrence of depression) based on the Nagelkerke R Square indicators. If independent variable were used in predicting the occurrence of depression, 85% of those cases would be correct. According to the model, depression affects men more. Respectively, men are 7.7 times likely to develop depression than women. Persons who had some sort of psychiatric disorder in the history were 5,9 times likely to develop depression. However, these interpretations are not reliable due to the width of confidence interval, as a direct result of a small sample size.

Correlation between two assessment instruments used in the study - MADRS and Zung Scales. The findings showed that there was a correlation between the assessment instruments in all tests. There was statistical significance ($p=0,001<0,05$) (Table 4).

4. DISCUSSION

This study showed that prior to treatment a seventh of the subjects in the treatment subgroup suffered from depressive symptomatology (13.3%), with the same number in the no treatment subgroup (13.3%). Furthermore, nearly half of the subjects (46.7%) displayed depressive symptomatology during interferon therapy (*IFN*). The degree of depression in subjects infected with chronic hepatitis C taking *IFN* varied from 0% *(6)* to middle and high values *(7),* and in some cases even more than 80% *(8).* However, there are other findings too. The *Elshahawi* study from 2011, which comprised 400 subjects, showed that 30% of the infected subjects who did not take interferon suffered from depression thus pointing to the importance of CHC on the manifestation of depression even in the absence of interferon (*9*). This broad spectrum and huge variation results may occur because of different approaches to methodology, including the use of instruments for the assessment of depressive disorder (*10).* In this study, depending on the time of manifestation, the highest level of depression in the PEG-IFN-α-2a subgroup was found after 8 weeks, while in the no treatment group a rise of depression was found after 4 and a decrease after 8 weeks. The only rationale for the increase in depression in the subgroup with no treatment is a reactive state as a consequence of adjusting to and coping with the new situation (news of serious disease and awaiting treatment). Symptomatology in the context of adjustment disorder is highest in the first 4 weeks, followed by withdrawal of symptoms. Therefore, as far as the frequency of depressions is concerned, MADRS scoring has shown statistical significance between the subgroups after 4 and 8 weeks. On the other hand, findings on the frequency of depression on the Zung scale indicated there was statistical significance between the subgroups in all weeks. The explanation of difference in the frequency results between these two scales can be explained by the fact that the 'threshold' for the diagnosis of depression is lower on the Zung Scale. Respectively, the use of self-assessment scales could generate higher degrees of depression, mainly due to the "overvaluation" of symptomatology. Next, this study showed that the majority of the subjects infected with chronic hepatitis C were a younger population. Other findings *(11, 12)* also show that the majority of persons infected with CHC are in the third or fourth decade of their life. When it comes to the degree of depression, according to the MARDS Scale, mild depression was most present in both sub-

groups, with moderate depression less present and severe depression not present at all. According to the Zung Scale, both subgroups showed the signs of depression in remission, while a small number of subjects showed signs of severe depression requiring hospital treatment. This was expected since the method of item scaling differed between these two instruments. *Elshahawi* also in his study found that mild depression was the most prominent and severe depression least prominent form *(9).* The question is why are some persons with CHC more susceptible to depressive symptomatology during interferon treatment. Recognizing risk factors that lead to psychiatric adverse effects can help identify patients at a high risk and thus provide them with additional psychological assessment and support *(13).* Our study showed men are 7.7 times likely to develop depression than women. Gender difference is one of the most consistent findings in the prevalence and incidence in psychiatric epidemiology. Women are at a higher risk of developing depression. Gohier et al. studied the occurrence of depressive symptomatology in 71 CHC patients during and after interferon alpha treatment and found that the independent factor, which can be regarded as a predictor of interferon alpha caused depression, is female gender *(14).* However, there are conflicting findings proposed by Bonaccorso and Martin Santoz who found no difference in the occurrence of depression on gender match *(15, 7).*

Subsequently, this study showed that 46.7% of the subjects in the treatment subgroup had some sort of psychiatric disorder in the history, while this percentage was 53.3% in the no treatment subgroup. Psychiatric disorders which were recorded in history were as follows: anxiety disorders, personality disorders and abuse of PAS. Persons who had some sort of psychiatric disorder in the history were 5,9 times likely to develop depression. This can be explained by the fact that these persons are more vulnerable to different stressors (psychosocial stress, biological stress) or react to biological changes through psychiatric symptomatology. In an effort to determine depression risks, Lang carried out a study on assessing the safety of interferon treatment with CHC patients and he found out that the rate of psychiatric disorders was higher in those patients who had some sort of psychiatric disorder in their history (78%) *(16).*

For the assessment of depression, both types of instruments were used in the study (the MADRS and the ZUNG Scale). A correlation between the two scales was found in all tests across the subgroups. This was expected since there is usually a statistically significant correlation in the diagnosis of depression between these two scales, particularly in the assessment of the affect of depression and sleep as a relevant equivalent of depressive symptom. Our findings concur with other studies that used a similar approach. *(17, 18).*

5. CONCLUSION

We found in our study that depression was more present in persons infected with chronic hepatitis C treated with pegylated interferon α-2a in combination with ribavirin compared to persons infected with the same virus but without treatment; mild depression was the most common form. Our study showed that male gender and psychiatric disorders in the history can be regarded as predictors of depression in patients with chronic hepatitis C receiving interferon treatment. We found that there was a high correlation between the assessment instruments. However, the deficiencies of the study are as follows: findings interpretations are not reliable due to a small sample size and short monitoring period of the study subgroups, which greatly affects the hypothesis that depression is a direct result of interferon treatment.

- **Acknowledgments:** The authors have no proprietary or commercial interest in any materials discussed in this article.

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