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DEPRESSION DISORDERS IN PATIENTS WITH CHRONIC HEPATITIS C

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SUMMARY

Background: *Chronic hepatitis C was until recently treated with a combined therapy of interferon and ribavirin. More recently, direct antiviral agents (DAA), are being introduced. They are more tolerable and have fewer side effects, with better treatment results. In the Federation of Bosnia and Herzegovina we have started using this new therapy, with a limited financial opportunity. Large numbers of patients with chronic hepatitis C are former or current addicts, some of them treat their addiction with methadone or buprenorphine. These patients often formerly have a depression disorder and during treatment of chronic hepatitis need supervision of a psychiatrist, due to one of the side effects of interferon being deterioration of depression. Using this research we wanted to valorize the depression disorder of our patients, to indicate the effects of interferon on depression deterioration and the need for a new therapy protocol.*

Subjects and methods: *Examinees were patients with chronic hepatitis C on interferon therapy, which we divided into three groups: those who were never addicts, then the group of patients who were earlier addicts and have a long abstinence and patients who treat their addiction with a replacement therapy of methadone or buprenorphine. All patients completed Beck's test, which determines the level of depression, before and after interferon therapy.*

Results: *Patients who used to be addicts or were on replacement therapy had mild or moderate depression before interferon treatment in a large number. After interferon therapy, there was a statistically substantial increase of patients with serious depression, which was not noted before the therapy.*

Conclusion: *Interferon therapy deteriorates depression in patients with chronic hepatitis C and there should be a strive for new therapies with less side effects in treatment. No patients stopped therapy. That is a result of community work and supervision over patients from both hepatologists and psychiatrists.*

Key words: *hepatitis C - depression - interferon - addicts*

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INTRODUCTION

Chronic hepatitis C today is one of the most significant clinical and public health problems. As a large number of patients have no specific symptoms, patients do not even know about the disease and start treatment late, which leads to the occurrence of complications in the disease in the form of liver cirrhosis and/or hepatocellular cancer. Unrecognized hepatitis C leads to later spread of the disease and a larger number of those afflicted (Vukobrat-Bijedic 2008, Lupi 2006, Vucelic 2003, Ahmetagic 2011).

Until recently, the disease was globally treated with a combined therapy of pegylated interferon and ribavirin, while today we have a rise of the "interferon free" therapy, with the new, so called, direct acting antiviral agents. Even so, most countries still do not have the possibility of introducing this new therapy, which is expensive and often unavailable.

Recent studies show a significantly better tolerance of the DAA therapy with less side effects in regards to the interferon and ribavirin therapy, which decreases the number of therapy breaks and increases the number of cured patients. These studies show a larger efficiency of this therapy and the need to introduce it (Ioannou 2018, Hong 2018).

A significant number of patients with chronic hepatitis C belong to the intravenous (i.v.) group of addicts, as the disease is most commonly spread through the parenteral way, in this case with the mutual use of infected needles and syringes.

Today a large number of patients treated with chronic hepatitis C are i.v. addicts, which have already stopped using narcotics or are on a continuing replacement therapy with synthetic narcotics methadone and buprenorphine. Research show that these patients have good treatment results and do not fall behind with other groups of patients (Midgard 2016, Waizmann 2010, Belfiori 2009). New studies show an even better efficiency of DAA drugs with this group of patients along with a significantly smaller number of side effects (Scherz 2018, Grebely 2018, Boglione 2017, Dore 2016).

Methadone is a synthetic opioid, a strong pain reliever. By composition it is a hydrochloride and success-

fully works on morphine receptors in the brain, where 1 mg of methadone substitutes and achieves the effect of 4 mg of morphine. Because of that it is applied today as a replacement therapy with addicts, through the so called substitution, sings of abstinence crisis are eliminated. An addict, under the supervision of medical staff, gets a daily dose of methadone which maintains a normal state and a metabolic balance (Ali 2017, Toce 2018).

Buprenorphine is an opioid drug, which is not as strong as methadone, even though his effects can last longer. It blocks receptors, interfering with the abuse of heroin and other opioid pain relievers. Can be used once every two days (Martin 2018, Zoorob 2018).

Patients on the replacement therapy require constant supervision because of possible complications of the therapy, along with the possibility of repeated abuse of more serious narcotics (Serafini 2018, Lintzeris 2018).

Patients who have used narcotics before or are on the replacement therapy often have psychiatric disorders and take different drugs for mental health, especially antidepressants. Because of this, every single side effect, which is connected to deterioration of their mental status is very significant. Also, a psychiatrist judgement on the eventual correction or inclusion of preventive antidepressants during the time of the therapy is very important (Sarkar 2014, Ehret 2014, Udina 2014).

Interferons are natural proteins which produce immune system cells as a response to stimulation of foreign matter, such as viruses, parasites and tumor cells. They are part of the glycoprotein group, which are known as cytokines. Interferons are produced by a large number of cells as an answer to the presence of a double RNA molecule, which is a key indicator of a viral infection.

Interferon inhibited the replication of viruses in the host cell, activates NK cells (natural killer cells) and macrophages, increases the presence of antigen lymphocytes and the resistance of cells towards the viral infection.

Interferons are used as treatment for a large number of diseases, among viral infections like hepatitis C. Pegylated interferon is a special form of the molecule on which a molecule of polyethylene glycol is connected, so that the interferon`s effects last longer.

The most common side effects of interferon treatment are symptoms similar to those of the flu: elevated body temperature, fatigue, headaches, muscle pain, while nausea, depression, weight loss can also occur.

In some patient severe effects on their central nervous system have been noticed, especially depression, suicide thoughts and even suicide attempts during their interferon treatment. Also other side effects have been noticed like emotional liability, bipolar disorders, mania, changes of psychic state. These disorders are especially present at patients with a history of psychiatric disorders (Fialho 2018, Belvederi Murri 2017, Chiu 2017, Vabo 2016, Banjac 2016, MM 2015, Mahajan 2014, Udina 2012).

Because of all the above, patients have been especially supervised during interferon treatment, with which patients have great help from our psychiatrists, which have regularly followed them.

To valorize the depression disorders with these patients, which were the most common, all the patients completed before and after the treatment, Beck`s test, which determines the level of depression in patients.

This way we got the results, which will show us what the level of depression was in our patients, so we could get valuable data about later usage of interferon in the light of existence of new therapies, which by new research have no such side effects, but are often unavailable to our patients.

The goal of this paper is to establish an existence of depression in patients with chronic hepatitis C, along with the effects of pegylated interferon treatment on the level of depression with these patients.

SUBJECTS AND METHODS

Examinees

Examined causes in this paper were the patients, which have been treated at the Clinic for infectious diseases of the University clinic hospital Mostar (SKB Mostar) because of chronic hepatitis C. The examination was done from 01.01.2014. until 31.12.2017. and have been treated with pegylated interferon and ribavirin.

We received consent from every patient, before we started treatment, for the treatment and supervision during the treatment, which was approved by the Ethics committee of SKB Mostar.

Patients were infected with hepatitis C viruses genotype: 1a, 1b and 3. Those were the genotypes of the virus, which are the most common in our population. Genotyping is along with a level of viremia determined using a method of polymerase chain reaction (PCR), which we used on every patient. For those purposes the Abbot Real Time PCR M 2000 was used.

This examination included 90 examinees. From which 62 (68.9%) were male and 28 (31.1%) were female, which means there is statistically a larger number of males in this research.

The examinees were divided into three groups. The first group were patients that were never addicts and received chronic hepatitis C in a different way. The group included 24 patients. The second group was made of patients that were addicts, but have not taken narcotics for at least 12 months before the therapy. This group is made of 34 patients. The third group is made of 32 patients which apart from the chronic hepatitis C therapy take the replacement methadone or buprenorphine therapy during i.v. addiction treatment. Among the watched groups were no major statistical differences in the number of examinees (χ^2=1867, p=0.393) (Table 1).

Table 1. Structure of the sample

	N	%	χ^2	p
Sex			12.844	*<0.001*
Male	62	68.9		
Female	28	31.1		
Qualifications*			113.200	*<0.001*
ES	10	11.1		
HS	66	73.3		
CE	10	11.1		
UE	4	4.4		
Addiction			1.867	0.393
Was never an addict	24	26.7		
Supstitution	32	35.6		
Abstinent	34	37.8		
Genotype			32.267	*<0.001*
1a	30	33.3		
1b	8	8.9		
3	52	57.8		
Fibrosis stage			105.067	*<0.001*
0	2	2.2		
1	8	8.9		
2	28	31.1		
3	40	44.4		
4	6	6.7		
5	2	2.2		
6	4	4.4		
Beck 1			27.800	*<0.001*
No depression	52	57.8		
Mild depression	16	17.8		
Moderate depression	22	24.4		
Beck 2			36.400	*<0.001*
No depression	42	46.7		
Mild depression	12	13.3		
Moderate depression	30	33.3		
Heavy depression	6	6.7		

*ES - Elementary school; HS - High school;
CE - College education; UE - University education

Methods

All examinees were given Beck's test of depression level before the treatment, which they completed. Beck's test was developed and published 1961. (Beck et al. 1961.) Designed for quantification of depression levels. This evaluation allows an objective supervision of changes which occur over time and can be used during treatment. It is made of 21 questions, of which each has four answers, graded depending on the level of intension increase of symptoms (0-3 points). For quantification numbers need to be added next to the selected answer. After this, the results are quantified according to: 0-11 points no depression, 12-19 points is mild depression, 20-26 points is moderate depression and over 26 points is heavy depression. The questions are refer to mood disorders, loss of hope, feeling of rejection, inability to enjoy, sense of guilt, need for punishment, self- hatred, self judgement, suicide tendencies, tearfulness, irritability, disabilities in relations with other people, indecision, negative picture of themselves, inability to work, insomnia, tiredness, loss of appetite, weight loss, hypochondria and loss of libido (Filipčić 2008).

Therapy lasted, depending on virus genotype 6 or 12 months. The same questionnaire was completed after therapy ended.

We then compared the levels of depression in every examinee before and after therapy, calculated on the number of points, which valorized answers on the test.

We also compared the results in different groups of patients, to get data on levels of depression before and after therapy in every group, likewise between different groups

This way we received significant data on the effects of pegylated interferon on depression disorders in patients with chronic hepatitis C.

Statistical processing of data

Values of unprocessed data were inspected for normal distribution using Prism 5 software (GraphPad Software Inc.) and SPSS version 23 with the help of available tests for normality. Selection of corresponding tests depended on the number and distribution of subjects by group (χ^2 test over Fischer test), Kruskal Wallis test and Wilcoxon's test of range. Level $P<0.05$ was considered statistically significant (Puvacic & Puvacic 2004).

RESULTS

Genotype 1b was significantly the most present among examinees without dependence on anamnesis. In the beginning of testing the differences of levels of depression of mild depression were most in genotype 1a, while a moderate level was most present in genotype 3. There were no statistically significant differences in levels of depression during interferon treatment (Table 2).

Examinees with genotype 3 were achieving significantly higher results in the total BDI score before and after interferon treatment in relation to the other 2 genotypes, lowest results were achieved by examinees with genotype 1a on the scale of depression (Table 3).

Addicts were showing a significantly higher level of depression in the beginning of testing differences in the level of depression and after interferon treatment in regards to examinees who never had addiction in their anamnesis (Table 4).

Examinees on replacement therapy achieved significantly the highest results in total BDI score after interferon therapy in regards to abstinent and examinees who were not addicts while examinees who had no addictions in their anamnesis achieved the lowest results in total BDI score (Table 5).

Table 2. Structure of sample by viral genotype

	Genotype						χ^2	p
	1a		1b		3			
	N	%	N	%	N	%		
Beck 1							10.293	*0.025**
No depression	18	60.0	8	100.0	26	50.0		
Mild depression	8	26.7	0	0.0	8	15.4		
Moderate depression	4	13.3	0	0.0	18	34.6		
Beck 2							8.377	0.124*
No depression	16	53.3	6	75.0	20	38.5		
Mild depression	4	13.3	2	25.0	6	11.5		
Moderate depression	8	26.7	0	0.0	22	42.3		
Heavy depression	2	6.7	0	0.0	4	7.7		

*Fisher's exact test

Table 3. Differences in levels of depression in regards to the genotype

	Genotype						χ^2	p*
	1a		1b		3			
	M	IR	M	IR	M	IR		
Beck 1	4.00	16	8.50	7	14	15	6.429	*0.040*
Beck 2	12.00	19	10.50	10	19	19	7.205	*0.027*

*Kruskal Wallis Test

Table 4. Structure of sample by addiction anamnesis

	Addiction						χ^2	p
	Was not an addict		Substitution		Abstinent			
	N	%	N	%	N	%		
Beck 1							27.617	*<0.001**
No depression	24	100.0	12	37.5	16	47.1		
Mild depression	0	0.0	8	25.0	8	23.5		
Moderate	0	0.0	12	37.5	10	29.4		
Beck 2							32.344	*<0.001**
No depression	20	83.3	6	18.8	16	47.1		
Mild depression	4	16.7	4	12.5	4	11.8		
Moderate	0	0.0	18	56.2	12	35.3		
Heavy	0	0.0	4	12.5	2	5.9		

*Fisher's exact test

Table 5. Differences in levels of depression by addiction anamnesis

	Addiction						χ^2	p*
	Was not an addict		Substitution		Abstinent			
	M	IR	M	IR	M	IR		
Beck 1	3.50	6	17.50	11	15	17	3.723	0.054
Beck 2	6	8	25	13	18	19	6.776	*0.009*

*Kruskal Wallis Test

Examinees were achieving significantly higher total results on the BDI scale after interferon treatment in comparison to results in the beginning of the research (Table 6).

Table 6. Differences in total BDI score before and after interferon therapy

	$\bar{X}$	SD	Z	p*
Beck 1	11.04	7.929	-8.071	*<0.001*
Beck 2	16.16	9.664		

*Wilcoxon's test of range

DISCUSSION

Results of this research have showed a level of depression with each group of examined patients. Our goal was to show how the level and type of depression changes in patients following the end of the interferon therapy. Namely, we have clinically seen differences in patient behavior, which were on interferon therapy and we often needed a psychiatrist`s consultation, to change the dosage of the earlier therapy, include a depression disorder therapy or change an earlier existing therapy.

Results were shown using Beck`s test for qualification of depression levels, which patients completed before and after the therapy.

Patients, who were not i.v. addicts didn't have a depression disorder, nor did they develop one in a significant measure with the interferon therapy.

Patients who were earlier addicts and now are abstinent, as those who are on replacement therapy of methadone or buprenorphine had depression in significant numbers before the therapy began. As the therapy ended there were no statistically significant increases in numbers of patients with depression, but a number of patients appeared to have a heavy type of depression, which was not noted before the therapy began.

This means, there is a tendency, among a certain number of patients from the second and third group, of deterioration from milder to heavier types of depression.

Regarding the genotypes of patients, we noticed that most patients with mild depression had genotype 1a, while mild levels of depression were present among patients with genotype 3.

Many researches have been published in the world in the last few years about the effect of interferon on the appearance or deterioration of depression disorder among patients with chronic hepatitis C. All of those researches showed similar results. Interferon definitively leads to the appearance or deterioration of symptoms of depression among patients on interferon therapy, though, those deteriorations did not lead to disruption of therapy in a larger number (Huckans et al. 2015, Vabo et al 2016, Baeg et al. 2017, Fialho et al. 2018, Chiu et al 2017, Banjac et al 2016). Incidents of heavier depression disorders mainly hovered over 25-30% and was not in correlation with the results of the therapy (Vabo et al. 2016, Udina et al. 2012, Baeg et al 2017, MM et al. 2015). Heavier depression disorders during the therapy had shown mainly among patients who had earlier signs of depression, which we noted amongst our patients. (Mahajan et al. 2014, Belvederi Murri et al. 2017). These disorders mainly withdraw post therapy (Chiu et al. 2017, Huckans et al. 2015). We were unable to complete Beck's test six months after completed therapy as we planned earlier, due to incompliance from patients post therapy. Authors agree that a multidiscipline approach to such a patients and constant supervision is the most significant reason for a successfully finished therapy (Belfiori et al. 2009, Udina et al. 2012).

All our patients, who showed signs of depression or had a psychiatric disorder from before, were examined by a psychiatrist, who decided if the therapy should continue or change, to prevent serious symptoms of the illness. Research shows the advantages of preventive therapy among these patients, to avoid serious disorders (Sarkar & Schaefer 2014, Udina et al. 2014).

What is noteworthy, controls in our clinic were done once a week, patients would then under control of doctors receive an injection of interferon and a conversation was made every time, to establish if they had any new problems and to establish a need of an eventual extraordinary psychiatric control. Not one patients stopped the interferon therapy because of depression.

To evaluate depression among our patients, a continuous supervision is necessary after the therapy ended, which is less feasible, as this group of patients are not inclined to regular controls.

Further follows continuous tracking and evaluation of patients who are being treated with the new (DAA) therapy, after a certain time we will be able to come to a conclusion about the side effects and the success of this new therapy among our patients.

CONCLUSION

Patients with chronic hepatitis C, who have before taken narcotics or were still on replacement therapy of methadone and buprenorphine, had more often depression disorders in relation to patients who never took narcotics. After the interferon therapy ended, there was no significant increase in patients with depression disorders in the first two examined groups, but among abstinent appeared a few patients with a heavy level of depression. Among the group on replacement therapy there was a significant increase in patients with depression disorders in regards to the start of the treatment which was not noted before. Interferon therapy deteriorates depression in earlier addicts and especially patients on replacement therapy. None of our patients stopped therapy, which was a result of constant supervision and community work of the hepatologists and psychiatrists. The goal of treating chronic hepatitis C is curing the patient, but also a choice of therapy with as little side effects as possible.

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Contribution of individual authors:

Helien Bebek-Ivankovic: concept and design of the article; literature searches; writing and manuscript; approval of the final version.

Milenko Bevanda: revision of the manuscript; approval of the final version.

Bozo Susak: statistical analysis and manuscript preparation.

Svjetlana Grgic: literature research; comment of the draft paper.

Linda Soldo-Coric: literature research; manuscript preparation.

Jadranka Nikolic: involved with study design and data collection.

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