

DEPRESSIVE SYMPTOMS IN PATIENTS WITH HEPATITIS C TREATED WITH PEGYLATED INTERFERON ALPHA THERAPY: A 24-WEEK PROSPECTIVE STUDY

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SUMMARY

Objective: To prospectively evaluate depressive symptoms and risk factors for depression in patients with chronic hepatitis C (CHC) treated with pegylated interferon alpha therapy combined with oral ribavirin (PEG-IFN- α +RBV) and to analyze self-rating scale for depression in comparison to observer-based scale in the given population.

Subjects and methods: The Hamilton Depression Rating Scale and Zung Self Rating Depression Scale were used to screen for depressive symptoms in 74 subjects with CHC before PEG- IFN- α (mean dose 152.6 \pm 25.6 mcg), and in the follow-up visits (4, 12 and 24 week).

Results: Incidence of depressive symptoms in patients (mean age 39.9 \pm 13.4 years; equal sex distribution $p=0.225$) treated by PEG- IFN- α was the highest on 12th week of the treatment, when more than a 20% of our sample had moderate/severe symptoms of depression, and about 30% had minor depressive symptoms. For the screening of depression during PEG- IFN- α self-assessment scale was equally reliable as observer-based assesment of depressive symptoms. Common clinical parameters- subject related risk factors (age ($p=0.955$), sex ($p=0.008$), lifetime psychiatric disorder ($p=0.656$)), illness related risk factors (duration of CHC ($p=0.267$), i.v drug application as way of transmission ($p=0.292$)) and therapy-related risk factors (recommended duration of PEG-IFN- α ($p=0.993$) and dose of PEG-IFN- α ($p=0.841$)) were not significantly associated with depressive symptoms on PEG-IFN- α .

Conclusions: Liason-consultation services should collaborate with hepatologists in creating screening programmes, supplemented by objective criteria and guidelines, for early recognition and treatment of interferon-induced depression.

Key words: hepatitis C - interferon alpha - depressive symptoms - assessment

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INTRODUCTION

Chronic hepatitis C (CHC) is widely distributed blood-borne infection (Delić 2001). It is estimated that about 3% of the world's population have hepatitis C virus (HCV). There are about 4 million carriers Europe alone (Ghany et al. 2009). About 20% of patients infected with hepatitis C virus develops cirrhosis, and 1 to 4% of patients develop hepatic cellular carcinoma (Delić 2006).

Current standard treatment of CHC consists of pegylated recombinant interferon alpha (PEG- IFN- α) combined with oral ribavirin (RBV) (Nešić et al. 2004). Pegylated interferon is chemically modified recombinant interferon with an additional molecule of polyethylene - glycol, which increases its half life, improves antiviral efficiency, has fewer side effects, and the rate of viral response is increased from 10% to more than 50% (Ghany et al. 2009). The recommended duration of therapy with PEG- IFN- α + RBV is from 24 to 48 weeks (Ghany et al. 2009).

However, interferon treatment is associated with significant psychiatric side effects, such as: depressive mood, anhedonia, fatigue, anxiety, irritability, concentration difficulties, insomnia and suicidality (Nešić et al. 2004, Golden et al. 2005). In many patients, these side

effects are the main reason for the drug dose reduction or an early discontinuation of the treatment (Nešić et al. 2004).

It was inconsistently shown that certain risk factors contribute to the development of aforementioned psychiatric side effects, for example: sex (Nešić et al. 2004), ethnicity (Hauser et al. 2002), previous depressive episodes and suicidality (Raison et al. 2005), psychoactive substances abuse or dependence (Schaefer et al. 2008), other psychiatric disorders (Nešić et al. 2004, Raison et al. 2005), as well as duration of the treatment and dosage of PEG- IFN- α (Hosoda et al. 2000).

Screening for depressive symptoms in non-psychiatric medical settings is rather exception that routine, and in a high proportion of patients depression is neither recognized nor treated adequately (Davidson et al. 1999, Uzun et al. 2009).

The first steps in early recognition of depression during PEG- IFN- α will be adequate symptom assessment and a consideration of the risk factors. The symptom assesment could take the advantage of self-report questionnaires, which require little training and do not take much clinician time to administer and score, but studies which directly compared observer-based instruments for depression during PEG- IFN- α therapy with self rating scales in given population are rare.

The goal of the present study was to evaluate incidence and severity of depressive symptoms in patients with chronic hepatitis C treated with pegylated interferon alpha treatment combined with oral ribavirin prospectively during 24 week, to analyze risk factors for this side effect and to examine if self-rating scale for depression was adequate for the assessment of depressive symptoms in comparison to observer-based scale in the given population.

SUBJECTS AND METHODS

Subjects

From September 2008 to January 2010, 87 patients with chronic hepatitis C who were candidates for PEG-IFN- α therapy at the Institute of Infectious and Tropical Diseases "Prof. Dr Kosta Todorovic" Clinical Center of Serbia in Belgrade were contacted to participate. After screening, 13 of them were not included in the study-11 subjects had some of exclusion criteria and 2 subjects did not agree to participate. The study included 74 subjects (39 male and 35 female) aged 18-65 years (mean age (SD) 39.9(13.4) years) who agreed to participate and gave written informed consent.

For CHC diagnosis, we used multiple criteria:

- positive anti-HCV antibody (Elisa method) (Younossi et al. 1996);
- positive serum HCV RNK (by RT-PCR method) (Park et al. 2010);
- liver biopsy (blind aspiration) (Goodman et al. 1995),
- increased level of serum alanin aminotransferaze >1.5 times (ALT \geq 45 U/L) (Nešić et al. 2004);
- variations bilirubin and protrombine time above the normal range (Nešić et al. 2004). Stage of the liver necrosis and fibrosis, was calculate according to Ishak with standard coloring (Goodman et al. 1995).

Genotype of HCV was established by the genotypization method (Nešić et al. 2004), commercial testing based on amplification of HCV RNK.

Exclusion criteria were:

- other liver diseases (e.g. hepatic cellular carcinoma);
- serious cardiovascular diseases;
- current psychiatric illness or significant symptoms of depression;
- suicidal attempts in anamnesis;
- the use of psychoactive substances in the previous six months;
- dementia or other serious organic brain diseases
- serious neurological diseases (e.g. epilepsy);
- coinfection with hepatitis B or HIV;
- autoimmune diseases;
- the number of neutrofiles under 1,500/cm³ and the number of trombocytes platelet under 75,000/cm³.

Procedures

The sociodemographic and hepatitis C related history of the patients were examined on the basis of medical chart review.

Depressive symptoms were measured by observer rating scale -Hamilton Depression Rating Scale - HAMD (Hamilton 1960) and Self-Rating Depression Scale-ZSRDS (Zung 1965). The scale was administered by psychiatrist (the first author of this study). HAMD: 21 item HAMD score determines the severity of depression in the following way: less than 8 -without any depression, from 8 to 16 - minor depression, 17 and more moderate and severe depression.

ZSRDS: Maximum score on this scale is 80 if the values of item which are degreed from 1 to 4 are added up (rarely, sometimes, generally, most often). Depression is quantified based on the index of the (Zung 1965).

Baseline visit (T0) included rating of depressive symptoms by both scales. Then, PEG- IFN- α was prescribed in the dose recommended by hepatologist (mean 152.6 \pm 25.6 mcg, prescribed doses were: 90, 135, 180 mcg), duration (average 11.4 months). The subjects were followed up 24 weeks. Three follow up visits were performed: on the fourth week (T1), the twelfth (T2) and the twenty fourth week (T3) by the same rater and this visits included HAMD (Hamilton 1960) and ZSDRS (Zung 1965) assesment.

The study was approved by the Ethical Committee and carried out in accordance with the codex of good scientific practice of the School of Medicine, University Belgrade.

Statistical analysis

The database was created and analyzed using PASW Statistics 18 (SPSS inc. Chicago) The normality of distribution was tested with Kolmogorov-Smirnov test.

Continuous variables were presented as means \pm standard deviations and nominal variables were described using absolute and relative frequencies. Student t-test was used to test the difference of two means. Pearson. χ^2 -test was used to test the difference of frequencies. Pearson correlation coefficient was used to measure the association of HAMD and ZSRDS depression scores. Repeated measures analysis of variance (rmANOVA) was performed on serial data, using Greenhouse-Geisser correction for non-sphericity, when required. Pair-wise comparisons were performed using simple contrasts (baseline score as the reference group). Multivariate analysis of covariance (MANCOVA) and partial correlations were used to test the influence of risk factors on follow-up HAMD scores, after controlling for baseline scores.

RESULTS

All patients that entered the study (39 male and 35 female) completed the 24 week protocol. Table 1 shows variables of (out) patients included in the study.

Both sexes were equally distributed ($\chi^2(1)=1.47$, $p=0.225$), average age was (mean 39.9 ± 13.4 years). Females were significantly older than males ($t(100)=3.70$, $p<0.001$). Duration of CHC (period from the diagnosis established) was 4.2 ± 4.4 years. In majority of cases (52.7%) the transmission was unknown, while (27.0%) were infected by transfusion, 18.9% used a contaminated needle and 1.4% had intercourse related transmission. The duration of pegylated interferon combined with ribavirin therapy was 11.4 months, in the doses of 90, 135 and 180 mcg (mean 152.6 ± 25.6 mcg). About 30.0% had a lifetime psychiatric disorder.

Figure 1 shows distribution and severity of depressive symptoms at baseline, after four, twelve and twenty four weeks of the treatment.

Table 1. Baseline characteristics of the subjects with chronic hepatitis C

	Sample (n=74)
Age (years) mean \pm SD	39.9 \pm 13.4
Sex (male) (%)	52.7
Duration of CHC (years) mean \pm SD	4.2 \pm 4.4
Transmission of CHC (%)	
Blood transfusion	27.0
IV drug application	18.9
Sexual intercourse	1.4
Unknown	52.7
Recommended duration of PEG-IFN- α -2a (months) mean \pm SD	11.4 \pm 1.8
Dose of PEG-IFN- α (mcg) mean \pm SD	152.6 \pm 25.6
Lifetime psychiatric disorder (%)	31.1

^aCHC- Chronic hepatitis C;

^bPEG-IFN- α - Pegylated interferon alpha

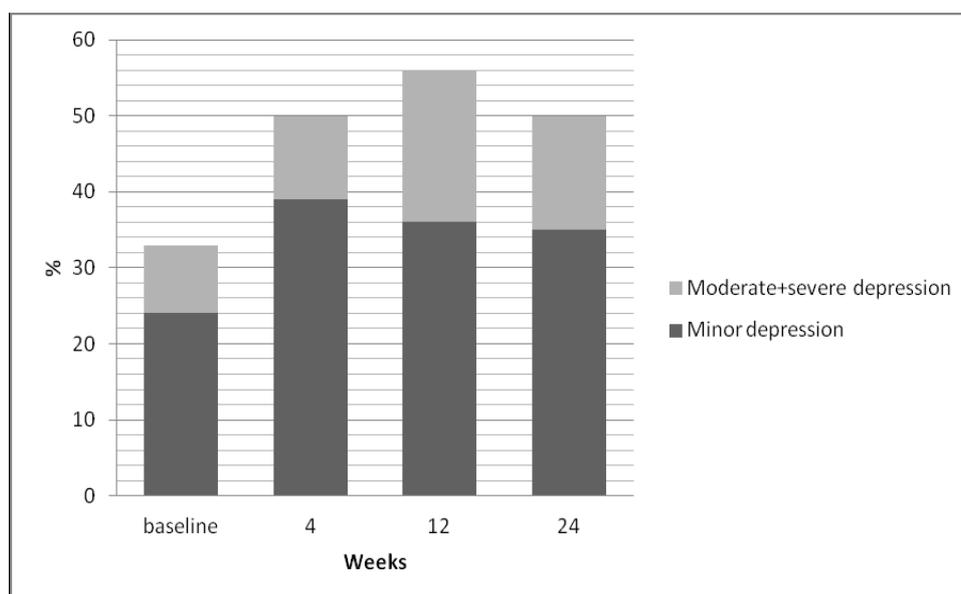


Figure 1. Distribution and the severity of depressive symptoms (minor, moderate and severe) according to HAMD scores (at baseline, 4, 12, and 24 weeks of PEG-IFN- α therapy)

The significant difference was found in HAMD scores at baseline and follow-up visits (FGreenhouse-Geisser(2,161)=11.39, $p<0.001$). Fourth, twelfth and twenty fourth week follow-up HAMD scores were significantly higher than HAMD score at baseline (F(1,73)=7.86, $p=0.006$; F(1,73)=30.23, $p<0.001$; F(1,73)=16.26, $p<0.001$, respectively).

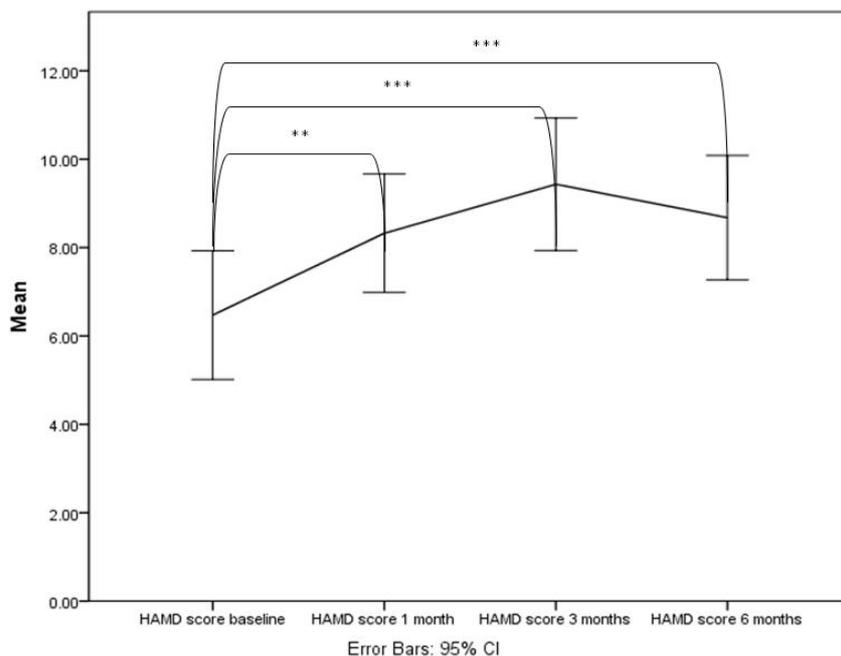
The same was true (Graph 3) for the self-assessment scale. Self-Rating Depression Scale scores increased during the first twelve weeks, and then values persisted to the end of the follow-up.

Self-Rating Depression Scale scores at the baseline and follow-up were significantly different (Fgreenhouse-Geisser(2,151)=3.51, $p=0.031$). The 12th and

24th week follow up Self-Rating Depression scores were significantly higher than given score at the baseline (F(1,72)=5.38, $p=0.023$; F(1,72)=6.63, $p=0.012$, respectively). The four weeks follow-up score was not significantly different from the baseline (F(1,72)=2.76, $p=0.101$).

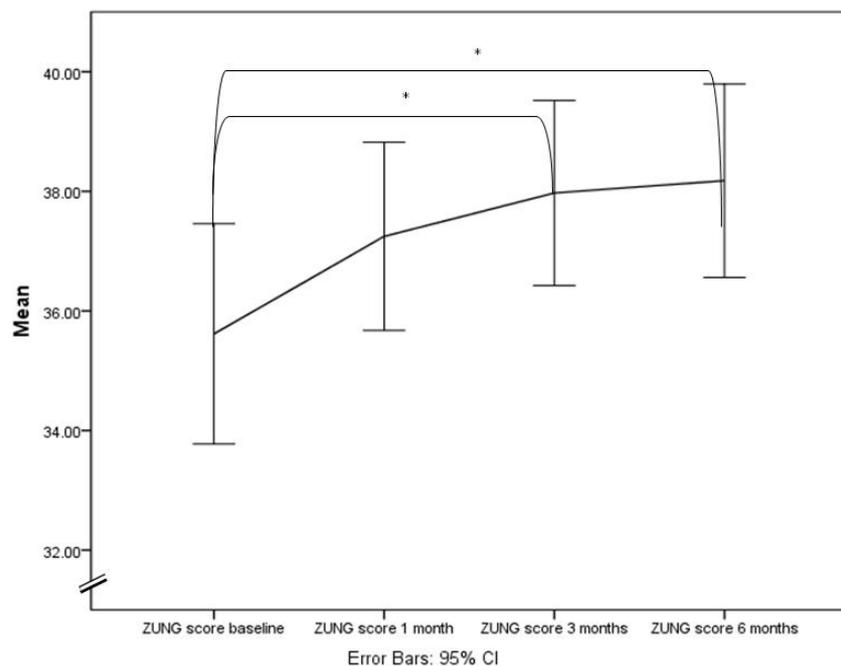
The scores of observer rating-Hamilton Depression Rating Scale (Hamilton 1960) and Self-Rating Depression Scale (Zung 1965) were highly statistically correlated both at the baseline and after 4, 12 and 24 weeks.

Multivariate analysis of covariance (MANCOVA) and partial correlations were used to test the influence of risk factors on follow-up HAMD scores.



p<0.01, *p<0.001; ^aHAMD-Hamilton Depression Rating Scale

Figure 2. HAMD scores - baseline, 4, 12 and 24 week of treatment



* p<0.05; ^aZSDRS-Zung Self-Depression Rating Scale

Figure 3. Scores ZSDRS - baseline, 4, 12 and 24 weeks of treatment

Table 2. Correlation between the two instruments

HAMD and ZSDRS score correlations	R (df=72)	P
Baseline	0.695	<0.001
4 weeks follow-up	0.593	<0.001
12 weeks follow-up	0.513	<0.001
24 weeks follow-up	0.560	<0.001

^aHAMD-Hamilton Depression Rating Scale; ^bZSDRS-Zung Self-Depression Rating Scale

After controlling for baseline HAMD scores, no association was found with any of three groups of risk factors: 1) subject related risk factors (age ($p=0.955$), sex ($p=0.008$))(the only exception included female sex as a risk factor for depression ($p=0.008$) at fourth week after baseline) lifetime psychiatric disorder ($p=0.656$),

2) illness related risk factors (duration of CHC ($p=0.267$), i.v drug application as way of transmission ($p=0.292$)) and 3) therapy-related risk factors (recommended duration of PEG- IFN- α ($p=0.993$) and dose of PEG- IFN- α ($p=0.841$)).

Table 3. Risk factors for depressive symptoms in patients with CHC on PEG-IFN- α therapy (after controlling for HAMD baseline)

	Multivariate test	
	F(3,69)	P
Sex	3.40	0.023*
Lifetime psychiatric disorder	0.54	0.656
IV drug addiction	1.27	0.292

	r (df=71)	P
Age	0.01	0.955
Duration of CHC	-0.13	0.267
Duration of interferon therapy	<-0.01	0.993
Dose PEG-IFN- α	-0.02	0.841

*more depressive symptoms in female on 4th week-visit (F (1,66) 7.524, $p=0.008$), but without sex differences on the other visits

^bCHC-chronic hepatitis C, ^cPEG-IFN- α Pegylated interferon alpha

^aHAMD-Hamilton Depression Rating Scale, ^bPEG-IFN- α -Pegylated interferon alpha

DISCUSSION

Chronic hepatitis C and depression

Our results showed significant level of depressive symptoms in persons with CHC before PEG- IFN- α (33.8%). This results is similar to other international studies that registered depression in 10 to 40% patients with chronic hepatitis C (Majeed et al. 2009, Orru et al. 2005, Grothe et al. 2005).

According to Lee et al. (1997), every fourth person with hepatitis C had depressive symptoms and about 60% of them required psychiatric treatment. The reasons for such high rate of depression in CHC patients was explained by either-biological factors (neuro-toxicity of HCV and numerous changes in the cerebral metabolism) (Weissenborn et al. 2009) or psycho-social factors (reaction to unfavourable CHC prognosis, negative expectation of the outcome, insufficient information about the disease and stigmatization, etc) (Harris 2009).

PEG-IFN- α , depression and the assessment

However, PEG-IFN- α treatment could trigger (or exacerbate) a depressive symptoms. Several studies showed that PEG-IFN- α was associated with depression in chronic myeloid leukemia (Mamman et al. 2009), malignant melanoma (Navinés et al. 2009) and kidney cell carcinoma (Sakamoto et al. 2000). In CHC, interferon associated depression was shown by several studies (Schaefer et al. 2002, Diepernik et al. 2000).

The incidence of possible major depressive disorder was very high according to Reinchenberg et al. (2005), who performed 72-week prospective study, showing that even 82% of interferon-treated patients developed

severe enough depressive symptoms to meet the CES-D criteria for possible major depressive disorder. However, by using both the Structured Clinical Interview for DSM-IV (SCID) and self-report questionnaires in twenty-three initially euthymic adults undergoing year-long PEG-IFN- α treatment for hepatitis, Lotrich et al. (2007) showed that thirty-nine percent of euthymic subjects developed major depressive disorder.

We found increase in overall HAMD scores and ZSRDS scores in all follow-up visits (4,12 and 24 weeks of the PEG-IFN- α therapy). After 12 weeks, more than a half of the patients had depressive symptoms: although the majority had minor depression (36.5%), moderate and severe intensity of depressive symptoms was shown in about 20% of our sample.

There are other results where incidence of interferon alfa-induced depression in patients with hepatitis C was identified in significantly lower percentage. So, Davis et al. (1998) found depression in 16%, and Pariente et al. (2002) found unspecified depressive disorder in 6%. Moreover, some studies do not confirmed the association between PEG-IFN- α treatment and depression in CHC. Davis (2001) did not found any difference in the rate of depression between the patients treated with interferone alpha and placebo group, and Mulder et al. (2000) shown that interferon treatment is not associated with neither onset nor worsening of psychiatric symptoms in patients with hepatitis C.

Inconsistence in methodological approaches, including the assessment of depression, could be one of the reasons for aforementioned inconsistency (Schaefer et al. 2007). By using both questioners (Hamilton Depression Rating Scale and Self-Rating Depression Scale) our study confirmed that there was a high degree of correlation between observer-rated and self-reported

assessment tools in CHC patients treated with PEG-IFN- α . According to our knowledge, this is one of rare studies that directly compared two scales in this specific patient population.

In our study the peak of Hamilton Depression Rating Scale and Self-Rating Depression Scale score was evident on 12 week treatment. Majority of the studies showed that the onset of depression on PEG-IFN- α was around 12 weeks of therapy. For example, Martin-Santoz et al. (2008) presented a prospective cohort of patients with CHC and they found that in more than 90% of the subjects with depression on PEG-IFN- α , the affective disorder appeared during the first 12 weeks. Bonaccorso et al. (2002) have been evaluated 30 patients affected by CHC using the DSM-IV criteria and the Montgomery Asberg Depression Rating Scale, and registered that 40.7 % were clinically depressive after 3 month treatment, while in a prospective study conducted by Hauser et al. (2002) using BDI, the frequency of depression was the highest between 6 and 22 weeks (median 12 weeks). The other studies came to similar results (Crone et al. 2003, Lotrich et al. 2007). However, there are results which show that the onset of depressive symptoms might be evident in the later stages i.e. 24-48 weeks (Fontana et al. 2008) or at the very beginning of the therapy, as on the 4th week of PEG-IFN- α (Beratis et al. 2005). In a prospective study on a large number of patients with chronic hepatitis C undergoing interferon-alpha therapy done by Horikawa et al. (2003), there was a tendency for major depression to occur more frequently in the earlier stage of treatment; of 23.2% patients who became depressed, 73.9 % developed depression during the first 8 weeks of the 24week PEG-IFN- α treatment period.

The exact mechanism of PEG-IFN- α associated depression is not known, but potential etiological factors include changes in: a) serotonergic transmission (interferon-alpha upregulates serotonin uptake and serotonin transporter messenger ribonucleic acid (mRNA) expression (Tsao et al. 2008) and modulates serotonin receptor 1A (5HT_{1A}) (Cai et al. 2005)); b) HPA function (dysregulation of hypothalamic-pituitary-adrenal activity and increased plasma cortisol levels (Altindag et al. 2001), changes in glucocorticoid receptor (Cai et al. 2005) etc.), or c) cytokine pathways (induction of secondary cytokines -IL-1, IL-2, IL-6 and tumor necrosis factor alfa (Bonaccorso et al. 2001)). Moreover, in neuroimaging studies, depression has been linked to decreased activation in the dorsolateral prefrontal cortex, a phenomenon that is also seen with IFN-alfa treatment (Matthews et al. 2004).

Risk factors for depression on PEG-IFN- α

It was proven that certain risk factors contribute to the appearance of depressive symptoms in CHC patients on PEG-IFN- α . The most association were reported for: subjects related risk factors (sex (Nešić et al. 2004), age (Raison et al. 2005), lifetime depression and/or suici-

dality (Raison et al. 2005), other psychiatric diseases (Raison et al. 2005)), illness related risk factors (duration of illness (Schaefer et al. 2008)), i.v psychoactive substances application as a way of transmission (Schaefer et al. 2008)) and the therapy related factors (recommended duration of treatment and dose of drug (Hosoda et al. 2000)).

Our study showed that female sex was the risk factor but only in the early phase of PEG-IFN- α treatment. No other factors were found to correlate with depressive symptomatology in CHC on PEG-IFN- α either at the initiation of the therapy, or during next 24 weeks in our sample.

Some studies pointed out sex differences in the incidence of depression in this population. Nešić et al. (2004) found that females had more psychiatric side effects at PEG-IFN- α . In contrary, Bonaccorso et al. (2002) and Martin-Santoz et al. (2008) did not found any differences in the PEG-IFN- α associated depression regarding the gender of participants.

Among our subjects, about 20% had lifetime i.v psychoactive substance abuse. Our results agree with results of Martin-Santoz et al. (2008), Hauser et al. (2002) and others studies which did not shown association between psychoactive substances abuse and appearance of depressive symptoms. Nevertheless, a lot of studies pointed out that these persons were exposed to greater risk to develop depression (Lotrich et al. 2007, Schaefer et al. 2007) under the interferon therapy.

Moreover, although some studies (Edlin et al. 2001, Schaefer et al. 2005) showed that the lifetime psychiatric disorders were associated with depressive symptoms during PEG-IFN- α therapy, in our study and in many others (Davis et al.1998, Schaefer et al. 2007, Kraus et al. 2004, Obhrai et al. 2001) the association was not confirmed.

The other patients' characteristics at baseline (age, duration of the infection, duration of the treatment, and drug dosage) did not show considerable association with depression.

Limitations

Although we noticed the peak of depressive symptoms on 12 week on PEG-IFN- α therapy, it is important to continue observation of the patients for the whole duration of treatment i.e. during 48 weeks for those who were prescribed such therapy regimen. The design of the present study allow us to continue patients' follow up and further evaluation will be performed soon. However, the design of this study considered only routinely assessed risk factors as from the ordinary medical charts (sex, age, duration of CHC, transmission, PEG-IFN- α duration and dosis). In further research, particular attention should be focused on genetic/molecular risk factors like functional serotonin transporter gene polymorphism or functional polymorphisms in the interleukin-6 etc. By increasing knowledge about molecular mechanisms, clinicians will be enabled to

recognize individuals under higher risk and to prevent mood-related PEG-IFN- α side effects. Finally, very important question about drug choice for PEG-IFN- α associated depression was not discussed in this research, but the topic is beyond the scope of our present paper.

CONCLUSION

Incidence of depressive symptoms in CHC patients treated by PEG-IFN- α is the highest around 12th weeks of the treatment, when more than a 20% of our sample had moderate/severe symptoms of depression, and about 30% had minor depressive symptoms. For the screening of depression during PEG-IFN- α in non-psychiatric medical settings, hepatologists are encouraged to use self-assessment depression scale and not supported to rely on any of the routinely assessed risk-factors (patient related, illness related or the therapy related factors) since their predictive validity was shown as low.

Although simple and practical depression screening is helpful, it should be emphasized that screening and increased recognition alone are not sufficient, particularly in settings lacking systems to assure accurate diagnosis, effective treatment and careful follow-up. Screening programmes in hepatology should be supplemented by objective criteria and guidelines for the treatment of PEG-IFN- α induced depression in these patients and by the development of consultation-liaison services enabling a fruitful, mutual collaboration between hepatologists and mental health professionals.

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