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Development of Psychiatric Symptoms during Antiviral Therapy for Chronic Hepatitis C

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Abstract

Pegylated-interferon-α (Peg-IFN) are part of chronic hepatitis C (CHC) treatment. Among several side effects, it can induce psychiatric symptoms (PS) which could require discontinuation. The aim of this study was to evaluate the incidence, onset and risk factors of PS and antiviral treatment adherence in CHC patients treated with Peg-IFN plus ribavirin (RBV). All consecutive patients who received antiviral therapy between 2005 and 2011 were subjected to a psychiatric assessment before and during treatment. Of them, 49.2% reported PS especially during the first 4 weeks. Irritability was the predominant symptom recorded. The baseline factors associated with a higher risk of developing PS were: age ≤ 50 years (OR=1.67, 95% CI=1.15-2.43), living in Northern Italy (OR=1.88, 95% CI=1.31-2.70), genotype 1 (OR=1.82, 95% CI=1.28-2.60), previous antiviral treatment (OR=1.53, 95% CI=1.07-2.19) and history of mental disorders (MD) (OR=2.32, 95%CI=1.50-3.58). There was no difference in terms of sustained virologic response (SVR) between patients with and those without a history of MD (p=0.129). On the contrary, SVR was lower in patients who developed PS compared to other ones (p<0.001) due to the higher prevalence of difficult-to-treat patients. Only 1.7% of patients dropped-out for PS. In conclusion, most of patients receiving Peg-IFN develop PS, in particular irritability, especially during the first 4 weeks. Age ≤ 50, living in Northern Italy, genotype 1 infection, previous antiviral treatment and history of MD are associated with a higher chance of developing PS.

Keywords: Interferon; Adherence; Antiviral treatment; Hepatic disease; Mental disorders

Abbreviations

HCV: Hepatitis C Virus; Peg-IFN: Pegylated-Interferon-α; RBV: Ribavirin; DAAs: Direct Antiviral Agents; MD: Mental Disorders; PS: Psychiatric Symptoms; CHC: Chronic Hepatitis C; OR: Odds Ratios; CI: Confidence Intervals; SVR: Sustained Virologic Response

Introduction

Approximately 170 million people are infected with the hepatitis C virus (HCV) worldwide [1]. HCV infection is the most frequent cause of chronic hepatitis and an important risk factor for liver cirrhosis, end stage liver disease and hepatocellular carcinoma [2]. Treatment with Pegylated-interferon-α (Peg-IFN) and Ribavirin (RBV) associated or not with direct antiviral agents (DAAs), can lead to persistent eradication of HCV reducing rate of progression to end-stage liver disease and its complications [3]. An increased prevalence of mental disorders (MD) has been reported in HCV infection [4,5] and has been associated with the infection itself, possibly mediated by an effect on the central nervous system [2]. In addition, due to interaction of interferon and central nervous system [6-8], antiviral treatment is often associated with significant psychiatric symptoms (PS), such as depression, insomnia, anxiety, cognitive disturbances or suicide attempts [9,10]. In particular, depression rates during antiviral therapy range from 30 to 70% of cases [2,11-13]. The onset of PS during antiviral treatment has a strong impact on the quality of life and may affect treatment compliance leading to drug dose reduction or treatment discontinuation [11-13]. In order to avoid this even in patients with pre-existing MD and/or developing PS an adequate psychological and psychiatry counseling has been recommended [14]. Due to the scarcity of studies assessing the incidence of MD and PS during antiviral treatment in large cohorts of patients, we conducted this retrospective study to evaluate the incidence of psychiatric manifestations, their onset modalities, their impact on the adherence to and drop-out from antiviral treatment and the risk factors associated with development of PS in a large cohort of almost six-hundred patients with chronic hepatitis C (CHC) receiving Peg-IFN and RBV therapy at a single centre.

Methods and Patients

Selection of patient and data collection

All consecutive patients with CHC receiving Peg-IFN plus RBV treatment at our tertiary outpatient clinic for liver diseases at the Azienda Ospedaliero-Universitaria, Policlinico Sant'Orsola-Malpighi, Bologna, Italy between 2005 and 2011 were retrospectively enrolled in this study. The medical team consisted of both hepatologists and dedicated psychiatrists and psychologists experienced in the treatment of drug-induced psychiatric disorders. Each patient was evaluated by the same hepatologist for the entire duration of therapy. A telephone network was available for the management of patient's questions related to antiviral treatment. In that period, the standard of care was a combination of weekly subcutaneous Peg-IFN injections and daily weight-based oral RBV for genotypes 1 and 4 and fixed 800 mg RBV dose for genotypes 2 and 3 [15]. Two types of Peg-IFN were used: Peg-IFN 2a at dose of 180 mg/week (Pegasys, Hoffman-LaRoche, Nutley, NJ)

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and Peg-IFN 2b at dose of 1.5 mg/Kg/week (PegIntron, Merck/Schering Plough Corp., Whitehouse Station, NJ) [16]. The treatment duration was decided according to the standard clinical practice. Treatment stopping rules, in case of non-response, were applied following the international guidelines available in those years [17]. Patients were examined and monitored closely at the beginning of therapy, at weeks 4, 12, 24 (and also at weeks 36, 48 and 72 in patients treated for more than 24 weeks) and then followed for additional 24 weeks from the end of treatment. During the periodic visits, side effects were assessed and managed. Additional visits were scheduled to manage adverse events as needed. Data employed to perform this study were retrieved from an electronic data-base. Baseline data collected on each patient included: demographic characteristics, HCV genotype, presence of cirrhosis, type and duration of antiviral treatment, documented history of MD, PS arising during the treatment, date of symptoms onset. The presence of MD before treatment was defined according to patient's medical record and attending physician evaluation, while a history of MD leads to pre-treatment psychiatric consultation. The diagnosis of MD was made according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV TR) [18].

Statistical analysis

Continuous data were expressed as mean ± standard deviation, while categorical variables were summarized as absolute and relative frequencies. Non-parametric procedures were used to compare the characteristics of the patients, including Pearson chi-square test and Mann-Whitney U test. A p-value <0.05 was considered as statistically significant. Logistic regression models were used to evaluate possible predictors of development of PS and results were reported as odds ratios (OR) and their 95% confidence intervals (CI). All baseline characteristics were included in the univariate analysis. Covariates with a 2-sided P value <0.10 at univariate analysis were included for multivariate analysis. Backward stepwise elimination was used to remove non-significant factors from the model. All statistical analyses were performed using the SPSS software package (version 17.0 for Windows, SPSS Inc., Chicago, IL, USA).

Results

Characteristics of patients

Five hundred and ninety consecutive patients were included in this analysis. Baseline characteristics are summarized in Table 1. The mean age was 54 ± 13 years (range: 19-77) and most were males and came from Southern Italy. When the study population was subdivided in deciles, a higher prevalence of patients aged 51-60 years (27.6%) and 61-70 (26.6%) was observed. Data about employment status was available in 481 patients: more than half reported a stable employment status (39.5% employees and 18.5% freelancers) while the remaining (42%) were unemployed. Most patients were non-cirrhotic (77.8%) and treatment naive (59.3%). HCV genotype 1 was predominant (52.9%). Determination of interleukin-28B polymorphism was available in 76 (12.9%) patients: CC 25%, CT 56.6%, TT 18.4%. Peg-IFN 2a and 2b were equally prescribed. The duration of treatment was >48 weeks in 29% of patients. A history of MD was present in 130 (22%) patients. The types of MD are reported in Table 1. Among patients with a positive psychiatric history, 57 (43.8%) had already been treated with interferon-based antiviral therapy.

Development of psychiatric symptoms during treatment

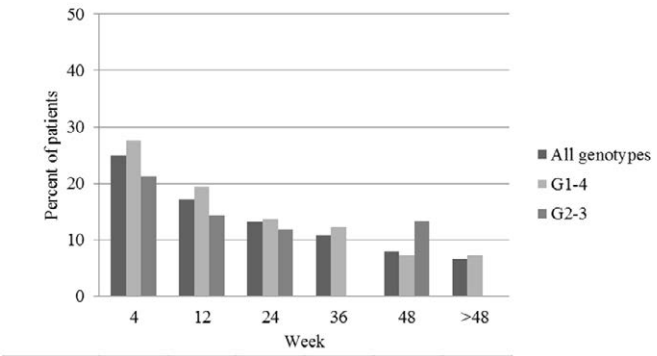
During the antiviral treatment 290 patients (49.2%) developed the following PS: Irritability (54.1%), sleep disorders (38.6%), depressed mood (35.8%), anxiety (22.8%), neurocognitive dysfunctions (12.4%), confusion (5.5%), psychotic manifestations (2.1%) and behavioral disorders (1%). Gender distribution, presence of cirrhosis and type of Peg-IFN used were similar between subjects who developed PS and those who did not develop PS. Mean age was lower in patients with PS, among whom the rate of patients aged ≤ 50 years was significantly higher compared to those without PS (44.8% vs. 29.3%, respectively; p<0.001). The two groups also differed in term of history of MD, genotype distribution and treatment-experience. The development of PS was less frequent in patients who came from the southern Italy compared to those coming from the center or northern Italy; the incidence of PS was higher during the first 4 weeks of treatment (24.9%) and decreased progressively in the following weeks (Figure 1). The risk to develop PS was greater in patients with genotype 1 and 4 (Figure 1) and, as expected, in those with a history of MD (Figure 2). Irritability was the predominant symptom ranging from 40.8% to 54.3% of cases between week 4 and week 24 (Figure 3). Five baseline factors were associated with a higher chance of developing PS both at univariate and multivariate analysis: age ≤ 50 years, living in Northern Italy, genotype 1, previous antiviral treatment and history of MD (Table 2).

Treatment outcomes

Treatment was discontinued in 32/590 patients (5.4%): 22 patients (3.7%) for medical reasons and 10 (1.7%) for psychiatric complications, including also a case of completed suicide (0.2%) occurred in week 16. The rates of drop-out for psychiatric complications were higher in patients with than in those without MD history (4.6% vs. 0.9%, respectively; p=0.010). None of the patients with a history of psychiatric disorder induced by previous antiviral therapy dropped out during the new treatment course. Only eight subjects (1.4%) were lost during the follow-up. A sustained virologic response (SVR), defined as persistently negative HCV-RNA 24 weeks after end of treatment, was obtained in 353 patients (59.8%) while 95 (17.3%) did not respond to therapy and 102 (16.1%) had a viral relapse after treatment discontinuation. There was no SVR difference between patients with and those without a history of MD (53.8% vs. 61.5%, respectively; p=0.129).

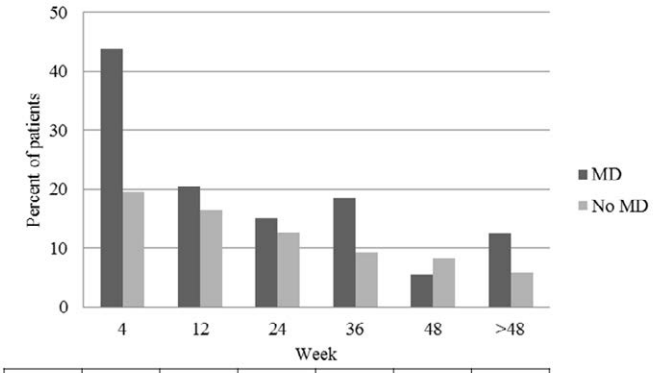
Age	54 ± 13
Male gender	316 (53.6)
Area of recruitment: ▪ Northern Italy ▪ Central Italy ▪ Southern Italy	 230 (39) 51 (8.6) 309 (52.4)
Genotype: ▪ 1 ▪ 2 ▪ 3 ▪ 4 ▪ 5 ▪ Mixed	 312 (52.9) 193 (32.7) 57 (9.7) 22 (3.7) 1 (0.2) 5 (0.8)
Cirrhosis	131 (22.2)
Previuos antiviral treatment	240 (40.7)
History of MD	130 (22)
Type of previous MD: ▪ Substance abuse ▪ Depression ▪ Anxiety ▪ Anxiety and depression ▪ Psychiatric disorder interferon-induced ▪ Bipolar disorder	 68 (52.3) 20 (15.4) 17 (13.1) 13 (10) 8 (6.2) 4 (3.1)
Type of Peg-IFN: ▪ 2a ▪ 2b	 305 (51.7) 285 (48.3)

Table 1: Baseline characteristics of the study population.



All genotypes	147/590	75/437	35/267	18/168	10/126	5/76
G1-4	95/340	47/242	26/191	18/147	8/111	5/69
G2-3	52/250	28/195	9/76	0/21	2/15	0/7

Figure 1: Incidence of psychiatric symptoms by weeks from start of antiviral treatment according genotype. Genotype 5 and mixed genotypes were included in G1-4 group. G: Genotype.



MD	57/130	15/73	7/46	5/27	1/18	1/8
No MD	90/460	60/364	28/221	13/141	9/108	4/68

Figure 2: Incidence of psychiatric symptoms by weeks from start of antiviral treatment according presence or absence of mental disorders. MD: Mental Disorders.

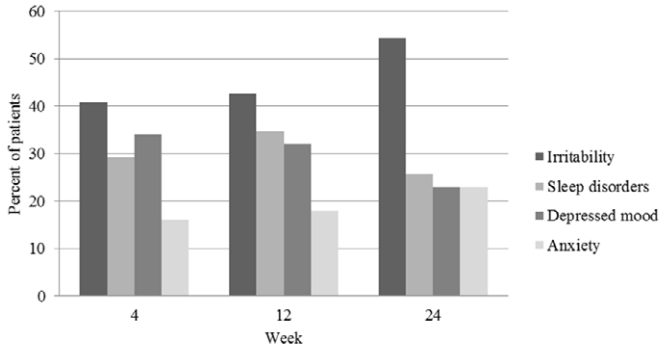


Figure 3: The most common psychiatric symptoms developed during the first 24 weeks of treatment with Pegylated-interferon-α and Ribavirin.

Conversely, the probability to achieve a SVR was significantly lower in patients who developed PS compared to those who did not (52.4% vs. 67%, respectively; p<0.001). However, this difference was related to the higher prevalence of most difficult-to-treat patients (genotype 1, cirrhosis and previous treatment failure) in PS group. Indeed, by selecting only patients with genotype 1, or with cirrhosis, or previously treated, the response rates were not statistically different (p=0.138, p=0.170, p=0.117, respectively) between the two groups.

Discussion

This retrospective analysis of a large cohort of Italian patients with CHC treated with Peg-IFN and RBV provides comprehensive information on the prevalence and course of PS occurring during antiviral therapy, which could be relevant for the management of this complication. However, we have to recognize that this study has limitations due to its retrospective nature. Moreover, the definition of MD was not based on structured interviews or screening instruments collected prospectively, but derived from the clinical judgment of attending physicians and patients self-reports. A high prevalence of MD history (although it may be underestimated) was found in our patients confirming the reports from previous studies that pointed out that the prevalence of psychiatric disorders in patients with hepatitis C was higher than in the general population [19,20]. Interferon-based antiviral treatments, by acting on this background, further enhance these abnormalities, so that up to 70% of HCV-infected patients treated with interferon have been reported to have mild to moderate depressive syndromes [2,21-23] and 20% to 40% have major depression [2,23]. Our report fully confirms these data.

As in previous studies [24] irritability was the symptom that more frequently occurred in our patients. As it is often under-appreciated and under-recognized [25], irritability needs to be carefully assessed and managed, since it correction would likely improve the quality of life of patient and adherence to antiviral therapy.

Based on the current literature, the most interferon-inducted adverse psychiatric effects occur during the first 3 months of therapy [26,27]. Our data confirm these observations as 50.7% of PS occurred during the first 4 weeks of treatment and more than 75% during the first 12 weeks. During this period patients with unfavorable genotype (1 or 4) and a history of MD are most at risk. For this reason it would be advisable to intensifying patient surveillance in the first 12 weeks of treatment in order to recognize and treat PS as early as possible, thus reducing drop-out risk. Our study also showed that the incidence of PS generally deemed to be more serious, such as confusion and psychotic symptoms, is low. This finding should encourage clinicians not to stop treatment when PS arise, even though close monitoring and caring by a multidisciplinary is warranted [14,28]. It should not be disregarded, however, that suicidal ideation and attempts, even if rare [29], remains a relevant risk in these patients as also shown by our study.

	Development of PS			
	Univariate		**Multivariate**	
	OR	**95% CI**	**OR**	**95%CI**
Age ≤ 50 years	**1.96**	**1.39-2.75**	**1.67**	**1.15-2.43**
Male gender	1.17	0.86-1.61		
Northern Italy	**2.05**	**1.47-2.87**	**1.88**	**1.31-2.70**
Genotype 1	**1.76**	**1.27-2.44**	**1.82**	**1.28-2.60**
Cirrhosis	1.46	0.99-2.16		
Previous antiviral treatment	**1.57**	**1.129-2.19**	**1.53**	**1.07-2.19**
History of MD	**2.80**	**1.85-4.23**	**2.32**	**1.50-3.58**
Peg-IFN 2a	1.11	0.81-1.54		

PS: Psychiatric Symptoms, OR: Odds Ratio, CI: Confidence Interval, MD: Mental Disorders, Peg-IFN: Pegylated-Interferon-α

Table 2: Univariate and multivariate analyses of factors associated with the development of psychiatric symptoms during antiviral therapy with Pegylated-interferon-α and Ribavirin.

Several risk factors for developing PS during Peg-IFN plus RBV treatment were identified in this study. Contrary to what has been described for depression [30,31], age has not emerged as a consistent risk factor in our study. However, by stratifying our population using 50 years as a cut-off, younger patients have a greater risk. Northern Italians have an almost 2-fold chance of developing PS with respect to subjects from Central and Southern Italy, probably due to different life-style and social relationships and/or a different support received by the family during treatment. In our study, genotype 1 is another significant predictive factor to develop PS, as reported in a previous study [32]. This is likely due to the need of higher doses of drugs, longer treatment duration and higher rates of previous interferon-based treatment. In fact, we found a higher risk for psychiatric disorders in previously-treated patients, suggesting that a further interferon treatment could favor an exacerbation of PS in patients with an increased vulnerability to psychiatric manifestations due to a previous interferon treatment. Conversely, the type of Peg-IFN did not influence the occurrence of PS. It should also be noted that PS occurred in half of our patients, with a greater frequency in those with a positive history of MD. Therefore, a history of MD and of PS development during previous interferon-based treatment should alert the clinician to institute a careful longitudinal evaluation of mood status. It has to be underlined, however, that, despite the development of PS, patients with history of MD are still able to complete their programmed treatment course as those with no history of MD. This result was likely achieved thanks to the multidisciplinary approach employed in this study, which involved dedicated physicians, psychiatrists, psychologists and nurses. Although the evaluation of the virologic response to treatment was not the main objective of this study, it is interesting to note that SVR did not differ between patients with and without a history of MD.

Therefore, also patients with psychiatric comorbidity, if highly motivated, might be included in an intensive psychiatric care program to prepare them for the antiviral treatment and should not be excluded a priori from HCV therapy.

On the contrary, patients who developed PS showed a lower rate of SVR. However, this was mostly due to the higher prevalence of difficult-to-treat patients in this group, rather than to a higher drop-out rate considering that only 1.7% of patients discontinued therapy because of psychiatric adverse effects (all within the first 24 weeks of treatment). A large number of new antiviral drugs have now been investigated and treatment regimens in the near future will not require the use of interferon thus a reduced incidence of treatment-induced PS can be expected. Nonetheless, these drugs will have very high costs and will not be available for all patients. Therefore, especially in developing countries, the replacement of interferon therapy by all-oral regimens will probably take time. In addition, the most recently approved DAAs will still be used in combination with Peg-IFN (e.g., in genotype 1) [33] suggesting that the interferon era is not yet over and that the psychiatric and psychological counseling will be still necessary.

In conclusion, patients with CHC, aged ≤ 50 years, living in Northern Italy, previously treated with antiviral therapy, with genotype 1 infection and/or history of MD have high risk of developing PS during Peg-IFN plus RBV treatment. Although irritability is often disregarded by physicians, this symptom occurs more frequently than depression in the first three months of treatment. A main message that can be derived from this study is that patients with a clinical history of MD should not be excluded from antiviral treatment and that a multidisciplinary approach to interferon-induced PS can avoid premature treatment discontinuation, thus offering to patient full chance to achieve a SVR to therapy.

References

1. Wasley A, Alter MJ (2000) Epidemiology of hepatitis C: Geographic differences and temporal trends. Semin Liver Dis 20: 1-16.
2. Schaefer M, Capuron L, Friebe A, Diez-Quevedo C, Robaeys G, et al. (2012) Hepatitis C infection, antiviral treatment and mental health: A European expert consensus statement. J Hepatol 57: 1379-1390.
3. Singal AG, Volk ML, Jensen D, Di Bisceglie AM, Schoenfeld PS (2010) A sustained viral response is associated with reduced liver-related morbidity and mortality in patients with hepatitis C virus. Clin Gastroenterol Hepatol 8: 280-288, 288.
4. Dinwiddie SH, Shicker L, Newman T (2003) Prevalence of hepatitis C among psychiatric patients in the public sector. Am J Psychiatry 160: 172-174.
5. Batista-Neves SC, Quarantini LC, de Almeida AG, Bressan RA, Lacerda AL, et al. (2008) High frequency of unrecognized mental disorders in HCV-infected patients. Gen Hosp Psychiatry 30: 80-82.
6. Raison CL, Borisov AS, Majer M, Drake DF, Pagnoni G, et al. (2009) Activation of central nervous system inflammatory pathways by interferon-alpha: Relationship to monoamines and depression. Biol Psychiatry 65: 296-303.
7. Capuron L, Pagnoni G, Demetrashvili M, Woolwine BJ, Nemeroff CB, et al. (2005) Anterior cingulate activation and error processing during interferon-alpha treatment. Biol Psychiatry 58: 190-196.
8. Shuto H, Kataoka Y, Horikawa T, Fujihara N, Oishi R (1997) Repeated interferon-alpha administration inhibits dopaminergic neural activity in the mouse brain. Brain Res 747: 348-351.
9. Taruschio G, Santarini F, Sica G, Dragoni C, Migliorini S, et al. (1996) Psychiatric disorders in hepatitis C virus related chronic liver disease. Gastroenterology 110: 1342A.
10. Dieperink E, Willenbring M, Ho SB (2000) Neuropsychiatric symptoms associated with hepatitis C and interferon alpha: A review. Am J Psychiatry 157: 867-876.
11. Schaefer M, Engelbrecht MA, Gut O, Fiebich BL, Bauer J, et al. (2002) Interferon alpha (IFNalpha) and psychiatric syndromes: A review. Prog Neuropsychopharmacol Biol Psychiatry 26: 731-746.
12. Leutscher PD, Lagging M, Buhl MR, Pedersen C, Norkrans G, et al. (2010) Evaluation of depression as a risk factor for treatment failure in chronic hepatitis C. Hepatology 52: 430-435.
13. Raison CL, Borisov AS, Broadwell SD, Capuron L, Woolwine BJ, et al. (2005) Depression during pegylated interferon-alpha plus ribavirin therapy: prevalence and prediction. J Clin Psychiatry 66: 41-48.
14. Neri S, Bertino G, Petralia A, Giancarlo C, Rizzotto A, et al. (2010) A multidisciplinary therapeutic approach for reducing the risk of psychiatric side effects in patients with chronic hepatitis C treated with pegylated interferon Î± and ribavirin. J Clin Gastroenterol 44: e210-217.
15. Hadziyannis SJ, Sette H Jr, Morgan TR, Balan V, Diago M, et al. (2004) Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: A randomized study of treatment duration and ribavirin dose. Ann Intern Med 140: 346-355.
16. Zeuzem S, Welsch C, Herrmann E (2003) Pharmacokinetics of peginterferons. Semin Liver Dis 23 Suppl 1: 23-28.
17. Ghany MG, Strader DB, Thomas DL, Seeff LB; American Association for the Study of Liver Diseases (2009) Diagnosis, management, and treatment of hepatitis C: An update. Hepatology 49: 1335-1374.
18. American Psychological Association (2000) Diagnostic and statistical manual of mental disorders: DSM-IV-TR. (4th eds): American Psychiatric Pub.
19. Butt AA, Khan UA, McGinnis KA, Skanderson M, Kent Kwoh C (2007) Co-morbid medical and psychiatric illness and substance abuse in HCV-infected and uninfected veterans. J Viral Hepat 14: 890-896.
20. Yovtcheva SP, Rifai MA, Moles JK, Van der Linden BJ (2001) Psychiatric comorbidity among hepatitis C-positive patients. Psychosomatics 42: 411-415.
21. Reichenberg A, Gorman JM, Dieterich DT (2005) Interferon-induced depression and cognitive impairment in hepatitis C virus patients: A 72 week prospective study. AIDS 19 Suppl 3: S174-178.
22. Schaefer M, Schwaiger M, Garkisch AS, Pich M, Hinzpeter A, et al. (2005) Prevention of interferon-alpha associated depression in psychiatric risk patients with chronic hepatitis C. J Hepatol 42: 793-798.

23. Schäfer A, Wittchen HU, Seufert J, Kraus MR (2007) Methodological approaches in the assessment of interferon-alfa-induced depression in patients with chronic hepatitis C - a critical review. Int J Methods Psychiatr Res 16: 186-201.

24. Schaefer M, Schmidt F, Folwaczny C, Lorenz R, Martin G, et al. (2003) Adherence and mental side effects during hepatitis C treatment with interferon alfa and ribavirin in psychiatric risk groups. Hepatology 37: 443-451.

25. Blacklaws H, Gardner A, Usher K (2011) Irritability: An underappreciated side effect of interferon treatment for chronic hepatitis C? J Clin Nurs 20: 1215-1224.

26. Loftis JM, Hauser P (2004) The phenomenology and treatment of interferon-induced depression. J Affect Disord 82: 175-190.

27. Hauser P, Khosla J, Aurora H, Laurin J, Kling MA, et al. (2002) A prospective study of the incidence and open-label treatment of interferon-induced major depressive disorder in patients with hepatitis C. Mol Psychiatry 7: 942-947.

28. Schäfer A, Scheurlen M, Kraus MR (2012) Managing psychiatric side effects of antiviral therapy in chronic hepatitis C. Z Gastroenterol 50: 1108-1113.

29. Fattovich G, Giustina G, Favarato S, Ruol A (1996) A survey of adverse events in 1,241 patients with chronic viral hepatitis treated with alfa interferon. J Hepatol 24: 38-47.

30. Miyaoka H, Otsubo T, Kamijima K, Ishii M, Onuki M, et al. (1999) Depression from interferon therapy in patients with hepatitis C. Am J Psychiatry 156: 1120.

31. Kraus MR, Schäfer A, Faller H, Csef H, Scheurlen M (2003) Psychiatric symptoms in patients with chronic hepatitis C receiving interferon alfa-2b therapy. J Clin Psychiatry 64: 708-714.

32. Martín-Santos R, Díez-Quevedo C, Castellví P, Navinés R, Miquel M, et al. (2008) De novo depression and anxiety disorders and influence on adherence during peginterferon-alpha-2a and ribavirin treatment in patients with hepatitis C. Aliment Pharmacol Ther 27: 257-265.

33. Kim do Y, Ahn SH, Han KH (2014) Emerging therapies for hepatitis C. Gut Liver 8: 471-479.