Original Contribution

Kurume Medical Journal, 59, 39-44, 2012

The Importance of a Prior Psychiatric Examination in Pegylated Interferon and Ribavirin Combination Treatment for Chronic Hepatitis C

KOICHIRO KUHARA, TATSUYA IDE, NAOHISA UCHIMURA*, RYUKICHI KUMASHIRO, TERUKO ARINAGA, ICHIRO MIYAJIMA, SHIRO MURASHIMA, KEI OGATA, REIICHIRO KUWAHARA, KEISUKE AMANO**, YUKARI FUJIMOTO**, KENJI SAKAI[†], KUNIHIDE ISHII[‡], YASUYO MORITA[§], MIKI SHIRACHI[§§] AND MICHIO SATA

*Department of Medicine and *Neuropsychiatry, Kurume University School of Medicine, Kurume 830-0011, **Yame General Hospital, Yame 834-0034, [†]Omuta City Hospital, Omuta 836-8567, [‡]Asakura Medical Association Hospital, Asakura 838-0069, [§]Nagata Hospital, Omuta 836-0862, [§§]Chikugo City Hospital, Chikugo 833-0041, Japan*

Received 8 November 2011, accepted 18 September 2012

Summary: Some patients receiving pegylated interferon and ribavirin treatment for chronic hepatitis C are forced to discontinue the treatment due to psychiatric disorders. We performed a retrospective study to evaluate whether pre-treatment psychiatric examinations could increase successful completion rates for this treatment. Methods: A total of 535 patients who started pegylated interferon-α-2b and ribavirin treatment at 6 hospitals affiliated with our hospital were included in this study. The patients were divided into two groups. Those who had visited a psychiatric clinic before treatment were Group A (N=223), and those who did not visit a psychiatric clinic before treatment were Group B (N=312). We analyzed the rate of discontinuation due to psychiatric disorders in the two groups. Results: The rate of discontinuation due to psychiatric disorders in Group A was found to be significantly lower than that of Group B (1.8% (4/223) vs. 6.1% (19/312), P=0.035). In Group A, 6.1% (4/65) discontinued the treatment due to psychiatric disorders, while the comparable rate in Group B was 27% (19/68) (P=0.0004). Among patients who presented with psychiatric symptoms during treatment, the rate of treatment completion was significantly higher in Group A than in Group B (69.2% (18/26) vs. 5.0% (1/20), P=0.0067). In patients with a history of psychiatric symptoms, no discontinuation due to psychiatric disorder was observed in Group A. Conclusions: A psychiatric examination before pegylated interferon and ribavirin treatment was found to positively contribute to the successful completion of the treatment.

Key words chronic hepatitis C, interferon, depression, prior psychiatric examination

INTRODUCTION

Chronic hepatitis C is a disease that can develop into liver cirrhosis and hepatocellular carcinoma (HCC), so it is important to prevent its progression and achieve a complete cure [1-4]. Recently, the therapeutic effectiveness of interferon treatment, which is the only treatment that can completely cure chronic hepatitis C, has been shown to increase when used in combination with ribavirin [5-8]. As interferon treatment has also been proven to reduce the risk of HCC [9-11], interferon treatment has been actively administered for chronic hepatitis C. However, interferon treatment has various adverse events that may prevent completion of the full treatment regimen. These include psychiatric adverse events, especially depression, which often leads to a discontinuation of interferon treatment [12-18]. The incidence of depression during the

Address correspondence to: Koichiro Kuhara, M.D., Division of Gastroenterology, Department of Medicine, Kurume University School of Medicine, 67 Asahi-machi, Kurume-shi, Fukuoka-ken 830-0011, Japan. Tel: +81-942-31-7561 Fax: +81-942-34-2623 E-mail: snb11332@nifty.com

Abbreviations: BDI, Beck's Depression Inventory; HADS, Hospital Anxiety and Depression Scale; HCC, hepatocellular carcinoma; SNRI, serotonin noradrenaline reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; SVR, sustained virological response.

pegylated interferon-α-2b and ribavirin combination treatment has been reported to range from 29 to 36% [5-7]. To treat depression, antidepressants such as selective serotonin reuptake inhibitor (SSRI), serotonin noradrenaline reuptake inhibitor (SNRI), and sulpiride have been shown to be effective [19-21]. However, especially in Japan, patients with no history of psychiatric disorders hesitate to seek psychiatric care after psychiatric adverse events develop. Moreover, even if patients do seek psychiatric care after psychiatric disorders develop, at that point it is often too late to complete the prescribed pegylated interferon and ribavirin combination treatment. We therefore have adapted our protocol to include a psychiatric examination before the start of pegylated interferon and ribavirin combination treatment. Accordingly, we examined retrospectively whether pre-treatment psychiatric examinations were associated with improved completion rates for the treatment.

METHODS

Patients

Five-hundred and thirty-five patients who started pegylated interferon-α-2b and ribavirin combination treatment at six hospitals affiliated with our hospital from January 2005 until August 2006 were included. They were divided into two groups. Patients who had visited a psychiatric clinic or hospital before the initiation of pegylated interferon and ribavirin combination treatment were classified as Group A, and patients who had not visited any psychiatric clinic or hospital before the initiation of the treatment were classified as Group B. A total of 223 patients were included in Group A, and 312 patients were included in Group B.

Comprehensive informed consent was obtained from all patients.

Psychiatric treatment

For the screening tests, the Hamilton Rating Scale for Depression [22] was used as a clinician rated scale, along with the Zung Self-rating Depression Scale [23]. The patients were comprehensively evaluated by these scales and psychiatric interviews. For cases that were assessed by a psychiatrist as having a high risk for developing psychiatric adverse events, prophylactic treatment, such as the oral administration of psychiatric medicines, was initiated before starting the pegylated interferon and ribavirin regimen. SSRI, SNRI, and sulpiride were used as antidepressant therapeutic agents. Furthermore, after pegylated interferon and ribavirin combination treatment was started, the psychiatrist performed medical examinations and administered treatment as required. Psychiatric adverse events were defined as depression, irritability, delirium and attempted suicide. Mild insomnia was not included as a psychiatric adverse event.

Genotype

Genotyping was performed by sequencing a portion of the 5' untranslated region of the HCV genome [24].

Pegylated interferon and ribavirin treatment

A combined treatment consisting of subcutaneous injection of 60–120 μg (1.5 μg per kg of body weight) of pegylated interferon-α-2b with daily oral administration of 600–1,000 mg (standard dosage per body weight) of ribavirin was performed. The period of administration was 48 weeks for genotype 1 and 24 weeks for genotype 2. We investigated and examined the reasons for discontinuation of the combination treatment as well as the course of psychiatric adverse events that developed after the treatment was initiated. After the end of the treatment protocol, the patients from both groups were followed-up for an additional 24 weeks. Sustained virological response (SVR) was defined as undetectable serum HCV-RNA levels by qualitative PCR at the end of the 24-week post-treatment follow-up period. Patients who did not meet these criteria were classified as non-SVR.

Statistical Analysis

Frequency was compared between the groups using the chi-square test with Yates's correction, or Fisher's exact test. The group means, presented as the mean values ± the standard deviations, were compared using the Mann-Whitney U- test. All reported P-values were two-sided, and P-values of <0.05 were considered to be significant.

Statistical analyses were performed using the JMP software program (SAS Inc., Cary, NC, USA).

RESULTS

Regarding the clinical background, no significant differences were observed in gender, age, or laboratory data between Groups A and B. However, Group A had a significantly larger number of cases with liver cirrhosis, HCC, and history of psychiatric disorders (Table 1). The incidences of psychiatric adverse events in Group A and Group B were 11.7% (26/223) and 6.4% (20/312), respectively, and the difference was not

significant. The psychiatric adverse events in Group A consisted of depression (18 cases), irritability (7 cases), and delirium (1 case). In Group B, 13 cases demonstrated depression, 5 cases showed irritability, and 2 cases experienced delirium. The average time at which such psychiatric adverse events initially developed was at week 11.4±7.6. All of the psychiatric symptoms appeared within 24 weeks. The percentage of cases in which pegylated interferon and ribavirin combination treatment was discontinued was 28.7% (65/223) in Group A and 21.8% (68/312) in Group B; this difference was not significant.

The most common reason for discontinuation of pegylated and ribavirin combination treatment in Group A was HCV-RNA positive finding at 24 weeks, followed by the development of HCC, interstitial pneumonia and fatigue. In Group B, the most common reason was the development of psychiatric adverse events, followed by an HCV-RNA positive finding at 24 weeks (Fig. 1). The percentage of cases discontinuing the treatment due to psychiatric adverse events was significantly lower in Group A (1.8%; 4/223) than in Group B (6.1%; 19/312) (P=0.035) (Fig. 2). Among all cases of discontinuation, the percentage of cases discontinuing the treatment due to psychiatric adverse events was significantly lower in Group A (6.1%; 4/65) than in Group B (27.9%; 19.68) (P=0.0004) (Fig. 1). As for the specific psychiatric adverse events that led to discontinuation, all 4 cases in Group A were due to depression. In Group B, 14 cases showed depression, 3 cases showed irritability, and 2 cases had delirium. There were no cases of suicide or attempted suicide in either group (Table 2). The completion rate of pegylated interferon and ribavirin combination treatment in cases that had developed psychiatric adverse events during the treatment was significantly higher in Group

TABLE 1.
Baseline Characteristics of the Study Population

	A Group (N=223)	B Group (N=312)	
Gender (Male: Female)	122:101	160:152	N.S.
Age (years)	57.1±9.5	58.3±9.6	N.S.
ALT (U/L)	73.5±46.8	79.2±74.9	N.S.
Hb (g/dL)	14.0±2.3	14.0±1.5	N.S.
Platelet ($\times 10^4/\mu L$)	15.1±4.8	15.3±5.3	N.S.
Genotype (1: 2)	201:21	253:42	N.S.
HCV-RNA level (KIU/mL)	1890±1482	1781±1471	N.S.
Stage (CH: LC)	180:43	286:26	P=0.0003
History of HCC	23	10	P=0.0014
History of Psychiatric Disorder	12	2	P=0.0013

ALT: Alanine Aminotransferase Hb: Hemoglobin
CH: Chronic Hepatitis LC: Liver Cirrhosis HCC: Hepatocellular Carcinoma

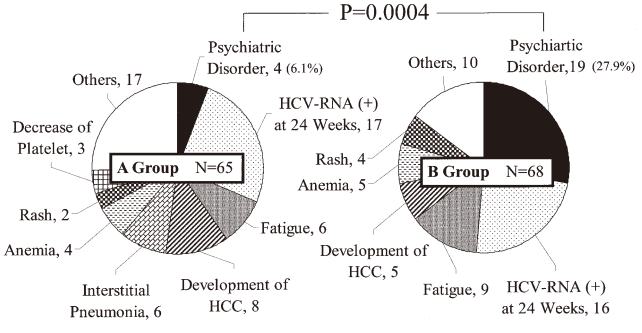

Fig. 1. Details regarding causes for discontinuing pegylated interferon and ribavirin combination treatment.

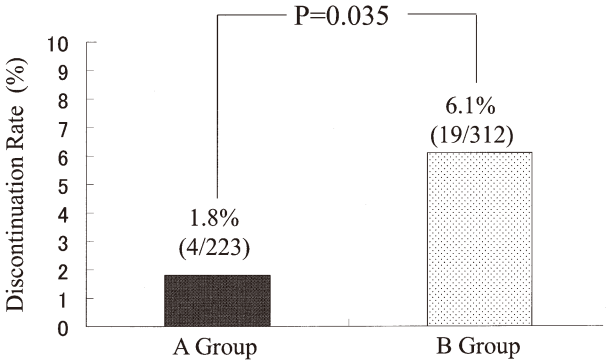

Fig. 2. Frequency of discontinuation of pegylated interferon and ribavirin combination treatment due to psychiatric disorders.

TABLE 2.
Detail of The Psychiatric Adverse Events Lead to A Discontinuation of Pegylated Interferon And Ribavirin Combination Treatment

	A Group	B Group
Depression	4	14
Irritability	0	3
Delirium	0	2
Attempted Suicide	0	0
Total	4	19

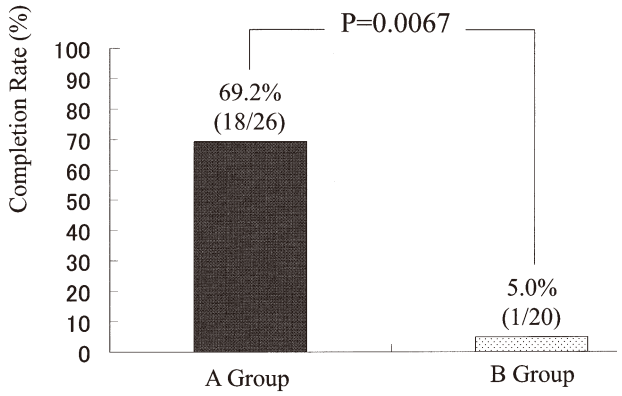

Fig. 3. Frequency of completing interferon in cases developing psychiatric adverse events during pegylated interferon and ribavirin combination treatment.

A (69.2%; 18/26) than in Group B (5.0%; 1/20) (P= 0.0067) (Fig. 3).

A total of 15 patients presented with a history of psychiatric disorders. Thirteen patients had a history of depression, 12 in Group A and 1 in Group B. One patient had a history of delirium. One patient had a history of panic disorder. Disease progression in cases with a history of depression (13 cases) is shown in Table 3 (Table 3).

Among the 12 patients with a history of depression in Group A, 6 patients (No.2, 3, 4, 7, 9, 10) were diagnosed as being at risk of developing depression due to interferon treatment, and 4 of these patients (No.2, 7, 9, 10) were prescribed psychiatric drugs. Of the six patients diagnosed as being at risk of depression, three patients (No.3, 4, 9) developed depression, but the depression was controlled in each case and there were no cases of discontinuation of interferon due to depression. On the other hand, the one patient (No.13) with a history of depression in Group B, started the interferon treatment without visiting a psychiatric clinic and was not prescribed any psychiatric drugs before starting treatment. During the course of treatment this patient developed depression and the interferon was discontinued in the second month after starting the treatment (Table 3). One patient in Group A had a history of delirium, and the type of sleeping medicine was changed based on the decision of a psychiatrist prior to the start of interferon treatment. During the

TABLE 3.
Disease Progression of Cases with a History of Depression

No	Group	Age	Gender	Psychiatric Examination before IFN	Risk of Depression (#1)	Psychiatric Drugs Initiation before the IFN Treatment	Development of Depression during the IFN Treatment	Discontinuation Caused by Depression
1	A	63	F	+	–	–	–	–
2	A	55	M	+	+	SSRI	–	–
3	A	51	M	+	+	–	+	–
4	A	40	F	+	+		+	–
5	A	53	M	+	–	–	–	–
6	A	57	F	+	–	–	–	–
7	A	51	F	+	+	SSRI sulpiride	–	–
8	A	43	M	+	–	–	–	–
9	A	57	F	+	+	sulpiride	+	–
10	A	54	M	+	+	SSRI	–	–
11	A	48	F	+	–	–	+	–
12	A	60	M	+	–	–	–	–
13	B	33	M	–		–	+	+

#1 Psychiatrists diagnosed

course of the interferon treatment, delirium was observed once but the treatment was completed successfully. The one patient with a history of panic disorder in Group A was prescribed benzodiazepine before starting the interferon treatment. This patient did not develop psychiatric symptoms during the course of the interferon treatment.

The SVR rates (Intention to treat analysis) in Group A and Group B were 42.6% (95/223) and 38.8% (121/312), respectively; this difference was not significant (P=0.374).

DISCUSSION

This study produced three important results. First, in Group A, the percentage of treatment discontinuation due to psychiatric adverse events was significantly lower than in Group B. Second, the rate of successful completion in cases where psychiatric adverse events developed during the treatment was significantly higher in Group A than in Group B. Third, pre-treatment psychiatric examinations were effective in improving pegylated interferon and ribavirin completion rates among patients with a prior history of psychiatric disorders. The following factors may be considered as possible reasons for these outcomes. The percentage of receiving psychiatric treatment in Japan is lower than that in other countries [25]. In Japan, most patients tend to reject such psychiatric examinations after the development of psychiatric adverse events. In Group A, patients had undergone a psychiatric examination before the start of the interferon treatment, so it may have been easier for these patients to agree to undergo a further psychiatric examination after the development of psychiatric adverse events. It is advantageous for psychiatrists to evaluate the premorbid disposition and mental state of a patient before the interferon treatment. In addition, such pretreatment examinations make it possible to begin administration of psychiatric medicines in high-risk cases as a preventive measure before starting interferon treatment. According to Shaefer, et al. [21] the administration of antidepressants such as a SSRI before interferon treatment was effective in preventing depression. Kraus, et al. [26] and Schaefer, et al. similarly reported that preventative administration of SSRI before starting interferon treatment it was effective in patients with depression or a history of depression. Schafer, et al. [27] reported no relation between the SVR rate and the development of depression. Loftis, et al. [28] reported that major depressive disorder induced interferon-α might be a predictor of a positive response to interferon-α therapy. However, if the interferon therapy is discontinued due to the development of depression, it is difficult to achieve SVR in these patients. Therefore, it is considered desirable to provide psychiatric treatment while carefully continuing the interferon treatment, even in cases in which depression develops. Our present findings suggest that all patients should receive psychiatric examinations before starting treatment. However, psychiatric examinations may be impossible in some cases due to a lack of psychiatric clinics or cost performance issues. In such cases, the Hamilton Rating Scale for Depression, and the Montgomery-Asberg Depression Rating Scale (MADRS) [29] may be useful as clinician rated scales, or the Zung Self-rating Depression Scale [27], Beck's Depression Inventory (BDI) [30], and Hospital Anxiety and Depression Scale (HADS) [31] may be useful as self-rating scales to evaluate the risk of psychiatric disorders. In this study, the SVR rate was not significantly higher in the pre-treatment group (Group A) than in the non pre-treatment group (Group B). This result can be explained by the fact that while discontinuation of treatment due to psychiatric adverse events was successfully reduced in Group A, this group contained a disproportionately high number of cirrhotic patients. Therefore, there were more cases of treatment discontinuation due to non-psychiatric reasons in Group A as compared with Group B, such as hepatic encephalopathy, or decreases in platelets or neutrocytes. Pavlovic Z et al. [32] suggested that hepatologists should collaborate with liaison-consultation services in creating screening programmes, supplemented by objective criteria and guidelines, for early recognition and treatment of interferon-induced depression. Looking ahead, we need to establish clear guidelines defining whether or not interferon treatment should be administered to high-risk patients with depression, along with clear criteria for discontinuation of the treatment.

REFERENCES

1. Alter MJ. Epidemiology of he patitis C. Hepatology 1997; 26:62S-65S.
2. Lauer GM, and Walker BD. Hepatitis C virus infection. N Engl J Med 2001; 345:41-52.
3. Poynard T, Yuen MF, Ratziu V, and Lai CL. Viral hepatitis C. Lancet. 2003; 362:2095-2100.
4. Shepard CW, Finelli L, and Alter MJ. Global epidemiology of hepatitis C virus infection. Lancet Infect Ds 2005; 5: 558-567.
5. Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 2002; 347:975-982.
6. Manns MP, McHutchison JG, Gordon SC, Rustgi VK,

Shiffman M et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet 2001; 358:958-965.
7. McHutchison JG, Gordon SC, Schiff ER, Shiffman ML, Lee WM et al. Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. Hepatitis Interventional Therapy Group. N Engl J Med 1998; 339:1485-1492.
8. Poynard T, Marcellin P, Lee SS, Niederau C, Minuk GS et al. Randomised trial of interferon alpha2b plus ribavirin for 48 weeks or for 24 weeks versus interferon alpha2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. International Hepatitis Interventional Therapy Group (IHIT). Lancet 1998; 352:1426-1432.
9. Hino K, Kitase A, Satoh Y, Fujiwara D, Yamaguchi Y, et al. Interferon retreatment reduces or delays the incidence of hepatocellular carcinoma in patients with chronic hepatitis C. J Viral Hepat 2002; 9:370-376.
10. Ikeda K, Arase Y, Saitoh S, Kobayashi M, Someya T et al. Anticarcinogenic impact of interferon on patients with chronic hepatitis C: a large-scale long-term study in a single center. Intervirology 2006; 49:82-90.
11. Takimoto M, Ohkoshi S, Ichida T, Takeda Y, Nomoto M et al. Interferon inhibits progression of liver fibrosis and reduces the risk of hepatocarcinogenesis in patients with chronic hepatitis C: a retrospective multicenter analysis of 652 patients. Dig Dis Sci 2002; 47:170-176.
12. Dieperink E, Willenbring M, and Ho SB. Neuropsychiatric symptoms associated with hepatitis C and interferon alpha: A review. Am J Psychiatry 2000; 157:867-876.
13. Hauser P, Khosla J, Aurora H, Laurin J, Kling MA et al. A prospective study of the incidence and open-label treatment of interferon-induced major depressive disorder in patients with hepatitis C. Mol Psychiatry 2002; 7: 942-947.
14. Horikawa N, Yamazaki T, Izumi N, and Uchihara M. Incidence and clinical course of major depression in patients with chronic hepatitis type C undergoing interferon-alpha therapy: a prospective study. Gen Hosp Psychiatry 2003; 25:34-38.
15. Loftis JM, and Hauser P. The phenomenology and treatment of interferon-induced depression. J Affect Disord 2004; 82:175-190.
16. Lotrich FE, Rabinovitz M, Gironda P, and Pollock BG. Depression following pegylated interferon-alpha: characteristics and vulnerability. J Psychosom Res 2007; 63:131-135.
17. Raison CL, Borisov AS, Broadwell SD, Capuron L, Woolwine BJ et al. Depression during pegylated interferon-alpha plus ribavirin therapy: prevalence and prediction. J Clin Psychiatry 2005; 66:41-48.
18. Scalori A, Pozzi M, Bellia V, Apale P, Santamaria G et al. Interferon-induced depression: prevalence and management. Dig Liver Dis 2005; 37:102-107.
19. Gleason OC, Fucci JC, Yates WR, and Philipsen MA. Preventing relapse of major depression during interferon-alpha therapy for hepatitis C--A pilot study. Dig Dis Sci 2007; 52:2557-2563.
20. Raison CL, Woolwine BJ, Demetrashvili MF, Borisov AS, Weinreib R et al. Paroxetine for prevention of depressive symptoms induced by interferon-alpha and ribavirin for hepatitis C. Aliment Pharmacol Ther 2007. 25:1163-1174.
21. Schaefer M, Schwaiger M, Garkisch AS, Pich M, Hinzpeter A et al. Prevention of interferon-alpha associated depression in psychiatric risk patients with chronic hepatitis C. J Hepatol. 2005; 42:793-798.
22. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960; 23:56-62.
23. Zung WW. A SELF-RATING DEPRESSION SCALE. Arch Gen Psychiatry 1965; 12:63-70.
24. Germer JJ, Rys PN, Thorvilson JN, and Persing DH. Determination of hepatitis C virus genotype by direct sequence analysis of products generated with the amplicor HCV test. J Clin Microbiol 1999; 37:2625-2630.
25. OECD Publishing, OECD Factbook 2009, P. 248-249. ISBN 978-92-64-0564-6
26. Kraus MR, Schafer A, Al-Taie O, and Scheurlen M. Prophylactic SSRI during interferon alpha re-therapy in patients with chronic hepatitis C and a history of interferon-induced depression. J Viral Hepat 2005; 12:96-100.
27. Schafer A, Scheurlen M, Weissbrich B, Schottker K, and Kraus MR. Sustained virological response in the antiviral therapy of chronic hepatitis C: is there a predictive value of interferon-induced depression? Chemotherapy 2007; 53:292-299.
28. Loftis JM, Socherman RE, Howell CD, Whitehead AJ, Hill JA et al. Association of interferon-alpha-induced depression and improved treatment response in patients with hepatitis C. Neurosci Lett 2004; 365:87-91.
29. Montgomery SA. and Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry 1979; 134:382-389.
30. Beck AT, Ward CH, Mendelson M, Mock J, and Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961; 4:561-571.
31. Zigmond AS, and Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983; 67:361-370.
32. Pavlovic Z, Delic D, Maric NP, Vukovic O, and Jasovic-Gasic M. Depressive symptoms in patients with hepatitis C treated with pegylated interferon alpha therapy: a 24 week prospective study. Psychiatr Danub 2011; 23:370-377.