Haematological abnormalities and quality of life in patients with chronic hepatitis C who meet major depression disorder during antiviral therapy

Alterazioni ematologiche e qualità della vita in pazienti con epatite cronica C che rispettano i criteri del disturbo depressivo maggiore durante terapia antivirale

G. Di Sciascio, S. Calò, M. Nardini

Department of Neurological and Psychiatric Sciences, University Hospital "Policlinico" of Bari

Summary

Introduction
Patients with chronic hepatitis C, during antiviral treatment, develop haematological and psychiatric side effects which negatively affect the health-related quality of life and compliance. The aims of this study were to investigate the correlation between haematological abnormalities, quality of life and antiviral treatment-induced depression.

Methods
We enrolled thirty-two patients with chronic hepatitis C who, before starting the antiviral treatment, were without any psychiatric disorder according to DSM-IV criteria. Data on health-related quality of life, depressive symptoms, laboratory values and socio-demographic characteristics were collected. Seven patients developed a Major Depressive Disorder after four weeks of antiviral therapy and started an antidepressant.

Results
All patients showed a significant impairment in health-related quality of life after four weeks of antiviral treatment (Table I). Patients who developed Major Depressive Disorder (G1 group) had more severe depressive symptoms, greater impairment on health-related quality of life, and higher haemoglobin levels than non-depressive patients (G2 group) (Table II). After eight weeks of antidepressant treatment, the G1 group showed significant reduction in depressive symptoms and significant improvement in physical functioning (Table V).

Conclusions
Anti-viral therapy is associated with haematological and psychiatric side effects along with diminished quality of life. Antidepressant treatment can reduce depressive and physical symptoms with an improvement in health-related quality of life.

Key words
Pegylated interferon alpha 2b • Ribavirin • Health-related quality of life • SSRI

Introduction

The antiviral therapy combined with pegylated interferon alfa 2b (Peg IFN-α-2b) and ribavirin (RBV) is one of the most effective treatment in patients with chronic hepatitis C, which can achieve an overall sustained viral eradication rate of 55% [1]. However, this therapy is associated with important hematological abnormalities [2] as anaemia and thrombocytopenia, and psychiatric adverse effects [2-4] as fatigue, anxiety and depression. These symptoms negatively affect patients through a significant impairment of health-related quality of life (HRQL). There is some evidence that patients who experience greater adverse effects and poorer HRQL are more likely to prematurely discontinue the treatment thus having a negative impact on virological response [5 6].

Correspondence:
Guido Di Sciascio, Department of Neurological and Psychiatric Sciences, University Hospital "Policlinico" of Bari, Bari, Italy • E-mail: guido.disciascio@gmail.com

Although the mechanisms of interferon induced depression remain poorly understood, the impact of interferon on corticotropin-releasing hormone (CRH)-mediated stress pathways and on Central Nervous System (CNS) serotonergic neurotransmission seems to be important [7 8]. Several studies report a correlation between reduced tryptophan levels and depression in patients receiving IFN-α and some data suggest a biochemical analogy between 5-HT metabolism in blood platelets and the CNS [9]. From these data, in recent years various studies have shown the effectiveness of SSRI in the treatment of interferon-induced depression as well as in their prophylactic use [10 11].

On the other hand, some authors report that most patients receiving IFNα do not develop clinically significant depression, especially when IFN-α is used in lower doses, or in pegylated preparations, suggesting that routine antidepressant pretreatment may expose a significant number of patients to an additional unnecessary medication burden [4]. Although generally benign, antidepressants are not without risks and adverse effects, especially in the medically ill who are often very susceptible to medication adverse effects. Thus, determining risk factors for the development of IFN-α induced depression, it might help identifying patients who most likely would benefit from close psychiatric follow-up and/or from antidepressant pretreatment.

Another interesting point of view is that depression is not only the depressed mood symptom, but rather a syndrome consisting of depressive, other psychological and physical symptoms that can present themselves in different combinations. Some authors observed that physical symptoms occurred early in IFN-α treatment and persisted, whereas depression-specific symptoms co-developed significantly later [12]. Finally, some data indicate that haematological abnormalities, as anaemia, during IFN-α treatment adversely affects social functioning [2-14].

This open study was aimed at elucidating the presence of haematological abnormalities and psychiatric side effects during IFN-α treatment in patients with chronic hepatitis C, their influence on HRQL and the effect of antidepressant treatment. Clinical and demographic risk factors of depression were also examined.

Methods

In this open prospective study between January 2007 and September 2007 (M/F, 21/11; mean ± SD, age = 45.81 ± 11.75 years; BMI = 26.36 ± 4.30; Peg IFN-α-2b dose = 130.17 ± 37.80 μg/week; RBV dose = 932.14 ± 210.91 mg/day), were enrolled thirty-two patients with chronic hepatitis C who were, according to DSM-IV criteria [15], without any psychiatric disorder before starting antiviral treatment with pegylated interferon alfa 2b and ribavirin. All patients gave their informed consent to participate in this prospective trial and the study was approved by the institutional ethical board of the University Hospital "Policlinico di Bari". Major depressive episodes during antiviral treatment were diagnosed by clinical assessment using the standardized clinical interview for DSM-IV Mental Disorders. In addition, we used the Hamilton Rating Scale for Depression-21 item (HRSD-21) [16] for the quantitative evaluation of depressive mood changes before and during antiviral treatment and the short-form 36 (SF-36) health survey was used to evaluate HRQL. The SF-36 [17] consists of 36 items measuring general health in eight domains: physical function, role limitations-physical, bodily pain, general health perceptions, vitality, social functioning, role limitations-emotional and mental health. Each scale has scores ranging from 0 to 100. SF-36 has good validity and reliability in chronic disease samples, including hepatitis C [2]. Baseline demographic, clinical and psychosocial data (age, gender, Peg IFN-α-2b and RBV dose, BMI and history of drug abuse) were collected; haemoglobin levels (Hb) and platelet count (PLT) data were also recorded.

Survey data were prospectively collected in a standardized manner before antiviral therapy began (T0); weeks 4 (T1) and 12 (T2) during treatment (Fig. 1). The diagnosis of major depressive episodes and HRSD-21 scores were evaluated by one senior psychiatrist who was blinded to the haematological parameters as well as to the psychiatric history of the patients.

After four weeks of antiviral therapy (T1) major depression was diagnosed by clinical assessment according to DSM-IV criteria in 7 patients out of 32 (21.87%). Patients who developed depression during antiviral therapy (Group 1) received an antidepressant treatment (paroxetine = 3, sertraline = 3, citalopram = 1) following the indications of a specialist in psychiatry.

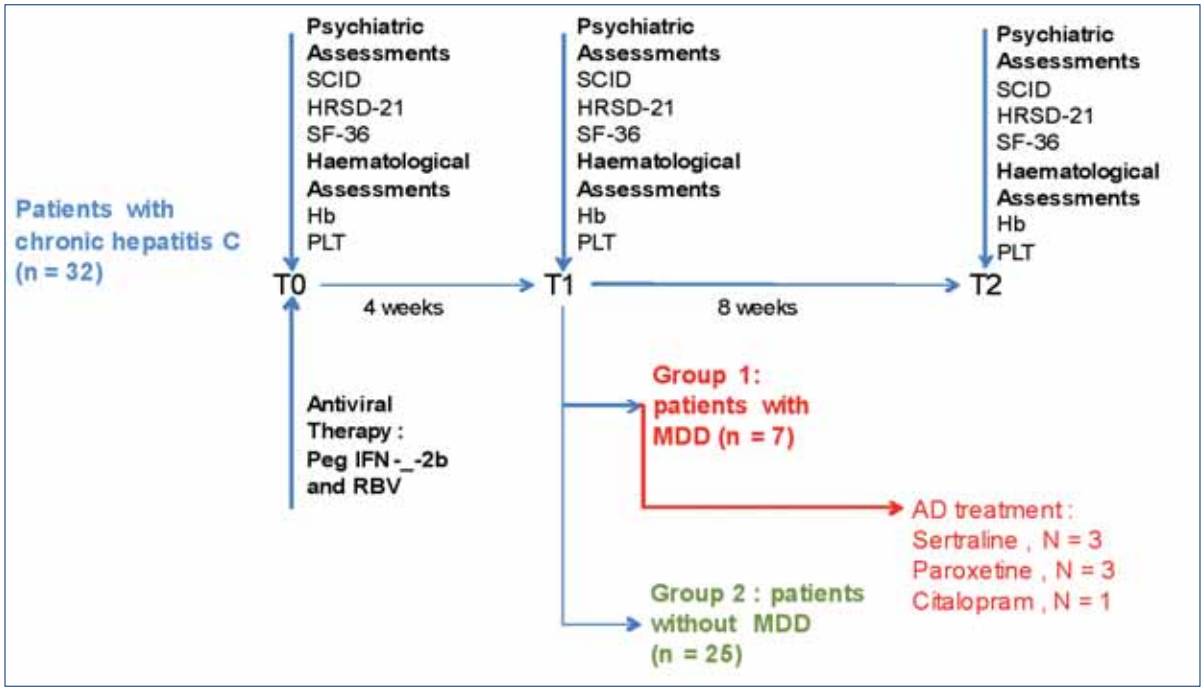

FIGURE 1
Study design. *Disegno dello studio.*

Statistical analysis was divided into four sections. Firstly, repeated measures ANOVA was used to examine changes in HRQL, HRSD-21 scores and haematological parameters (Hb and PLT) in all sample between T0 and T1. Secondly, one way ANOVA was used to evaluate the difference between patients who developed depression (Group 1) at T1 and the others (Group 2) on

TABLE I.
Changes in HRQL and HRSD-21 scores, and haematological parameters after 4 weeks of antiviral treatment (repeated measures ANOVA). *Modificazioni dei punteggi della HRQL e della HRSD-21 e dei parametri ematologici dopo 4 settimane di trattamento antivirale (ANOVA per misure ripetute).*

	T0 (mean ± SD)	T1 (mean ± SD)	p
Physical function	85.00 ± 6.80	68.21 ± 22.82	0.00107
Role limitations-physical	85.71 ± 24.93	35.71 ± 42.17	0.00000
Bodily pain	71.10 ± 24.07	47.32 ± 21.35	0.00001
General health perceptions	55.14 ± 9.67	47.25 ± 9.54	0.00208
Vitality	65.25 ± 12.59	45.71 ± 19.73	0.00000
Social functioning	79.64 ± 20.12	56.92 ± 25.28	0.00038
Role limitations-emotional	79.75 ± 33.18	44.07 ± 41.68	0.00014
Mental health	67.50 ± 17.70	54.10 ± 17.64	0.00192
HRSD-21	3.85 ± 2.81	10.21 ± 5.73	0.00001
PLT (mm^3)	177520.0 ± 52090.56	138840.0 ± 55430.65	0.00001
Hb (g/dl)	14.94 ± 1.51	13.32 ± 1.47	0.00000

HRQL, HRSD-21 scores and on haematological parameters. Thirdly, we analyzed the differences between the two groups (Group 1 *vs.* Group 2) at baseline (T0) as regards the psychiatric (HRQL, HRSD-21 scores) and haematological (Hb and PLT) assessments and the clinical and demographic parameters (age, Peg IFN-α-2b and RBV dose, BMI) using one way ANOVA. We also evaluated the difference between the two groups on history of drug abuse and previous antiviral treatment using Yates corrected chi-square tests (χ^2). Finally, in the fourth section we used repeated measures ANOVA to analyze changes in HRQL, HRSD-21 scores and haematological parameters (Hb and PLT) in the two groups between T1 and T2. For all analyses $p < 0.05$ was designated as statistically significant. Statistical analysis was carried out with the software Statistica 6 (StatSoft).

Results

Changes in HRQL, HRSD-21 scores and haematological parameters after 4 weeks of antiviral treatment

We observed, in all patients (n = 32), between T0 and T1, a statistically significantly increase ($p < 0.0001$) of HRSD-21 scores (3.85 ± 2.81 *vs.* 10.21 ± 5.73) with a statistically significantly impairment in HRQL (all $p = 0.00087$). Specifically we found a reduction in all SF-36 subscales with a greater impact on role limitations-physical, role limitations-emotional, social functioning, bodily pain and vitality (Table I). A statistically significantly reduction on Hb levels (14.94 ± 1.51 g/dl *vs.* 13.32 ± 1.47 g/dl) and PLT count 177520.0 ± 52090.56 *vs.* 138840.0 ± 55430.65) was also observed (Table I).

The association between major depressive disorder, HRQL and haematological abnormalities

When we compared the group of patients with a diagnosis of major depressive disorder after four weeks of antiviral treatment with the patients without depression (Group 1 *vs.* Group 2) we found in group 1 a statistically significantly ($p < 0.0001$) greater HRSD-21 score (17.66 ± 4.54 *vs.* 8.18 ± 4.13) and a statistically significantly ($p < 0.05$) lower scores on role limitations-physical (4.16 ± 10.20 *vs.* 44.31 ± 43.59), role limitations-emotional (11.00 ± 17.04 *vs.* 53.09 ± 42.03), vitality (25.00 ± 13.78 *vs.* 51.36 ± 17.33), social functioning (27.33 ± 9.47 *vs.* 65.00 ± 22.98), physical function (46.66 ± 12.11 *vs.* 74.09 ± 21.58) and mental health (34.66 ± 16.90 *vs.* 59.40 ± 13.95) than in Group 2 (Table II). We did not find any difference between the two groups as regards PLT count while Group 1 showed a statistically signifi-

TABLE II.
Scores on the HRQL and on the HRSD-21 and haematological parameters in the Group 1 and Group 2 at T1 (one way ANOVA). *Punteggi della HRQL e della HRSD-21 e dei parametri ematologici nei gruppi 1 e 2 al tempo T1 (ANOVA ad una via).*

	G1 (mean ± SD)	G2 (mean ± SD)	p
Physical function	46.66 ± 12.11	74.09 ± 21.58	0.00647
Role limitations-physical	4.16 ± 10.20	44.31 ± 43.59	0.03606
Bodily pain	32.66 ± 16.15	51.31 ± 21. 11	0.05614
General health perceptions	41.66 ± 6.05	48.77 ± 9.85	0.10706
Vitality	25.00 ± 13.78	51.36 ± 17.33	0.00205
Social functioning	27.33 ± 9.47	65.00 ± 22.98	0.00064
Role limitations-emotional	11.00 ± 17.04	53.09 ± 42.03	0.02531
Mental health	34.66 ± 16.90	59.40 ± 13.95	0.00105
HRSD-21	17.66 ± 4.54	8.18 ± 4.13	0.00005
PLT (mm^3)	108000.0 ± 28748.91	146550.0 ± 58260.28	0.169
Hb (g/dl)	14.68 ± 0.83	12.98 ± 1.40	0.018

TABLE III.
Scores on the HRQL and on the HRSD-21 scores and haematological parameters in the Group 1 and Group 2 at T0 (one way ANOVA) . *Punteggi della HRQL e della HRSD-21 e dei parametri ematologici nei gruppi 1 e 2 al tempo T0 (ANOVA ad una via).*

	G1 (mean ± SD)	G2 (mean ± SD)	p
Physical function	87.14 ± 5.66	84.40 ± 6.50	0.320
Role limitations-physical	89.28 ± 28.34	87.00 ± 22.95	0.826
Bodily pain	77.28 ± 24.23	71.44 ± 24.19	0.576
General health perceptions	58.71 ± 7.13	54.88 ± 9.74	0.342
Vitality	63.57 ± 19.73	67.40 ± 12.00	0.524
Social functioning	78.71 ± 23.59	81.16 ± 20.05	0.785
Role limitations-emotional	80.85 ± 32.69	80.00 ± 33.37	0.952
Mental health	66.85 ± 17.08	70.00 ± 19.44	0.702
HRSD-21	4.71 ± 3.30	3.44 ± 2.58	0.286
PLT (mm^3)	173200.0 ± 49251.40	183521.7 ± 53545.96	0.696
Hb (g/dl)	15.66 ± 0.79	14.85 ± 1.54	0.272

cantly higher Hb levels ($p < 0.01$) than Group 2 (14.68 ± 0.83 *vs.* 12.98 ± 1.40) (Table II).

Factors affecting HRQL and depression

We did not find any statistically significant differences ($p > 0.05$) between the two groups when we examined HRSD-21 and SF-36 subscale scores, haematological measurements (Table III) or clinical and demographic parameters (Table IV).

The effect of antidepressant treatment

In Group 1 between T1 and T2 (T1 *vs.* T2), after eight weeks of antidepressants treatment, we observed a significantly ($p < 0.001$) reduction of HRSD-21 scores (17.66 ± 4.54 *vs.* 4.83 ± 0.98) and a significantly ($p < 0.05$) improvement of social functioning (46.66 ± 12.11 *vs.* 77.33 ± 13.48), bodily pain (32.66 ± 16.15 *vs.* 70.83 ± 19.22) and general health perceptions scores (41.66 ± 6.05 *vs.* 53.16 ± 6.21). In this group we did not find any differences as regards the haematological parameters (Table V).
In Group 2 we did not observed any differences between T1 and T2 (T1 *vs* T2) as regards HRQL, HRSD-21 scores and PLT counts while we found a significantly ($p < 0.05$) reduction

TABLE IV.
Clinical and demographic parameters in the two groups. *Parametri clinici e demografici nei due gruppi.*

	G1 (mean ± SD)	G2 (mean ± SD)	p
Age† (years)	40.00 ± 4.28	47.44 ± 12.70	0.142
Peg IFN-α-2b† (μg/week)	128.33 ± 31.25	130.65 ± 39.95	0.896
RBV† (mg/day)	850.00 ± 388.58	954.54 ± 137.06	0.290
BMI†	27.78 ± 4.67	26.05 ± 4.26	0.426
History of substance abuse (number of patients)‡	3 (42.85%)	5 (20%)	0.458
Previous antiviral therapy (number of patients)‡	2 (28.57%)	7 (28%)	0.655

† one way ANOVA; ‡ Yates corrected chi-square tests (χ^2).

TABLE V.
Changes in HRQL and HRSD-21 scores, and haematological parameters; comparison between T1 and T2 in Group 1 (repeated measures ANOVA). *Confronto tra T1 e T2 delle modificazioni dei punteggi della HRQL e della HRSD-21 e dei parametri ematologici nel gruppo 1 (ANOVA per misure ripetute).*

	T1 (mean ± SD)	T2 (mean ± SD)	p
Physical function	46.66 ± 12.11	77.33 ± 13.48	0.00108
Role limitations-physical	4.16 ± 10.20	16.66 ± 30.27	0.36322
Bodily pain	32.66 ± 16.15	70.83 ± 19.22	0.00107
General health perceptions	41.66 ± 6.05	53.16 ± 6.21	0.02422
Vitality	25.00 ± 13.78	39.16 ± 18.00	0.28337
Social functioning	27.33 ± 9.47	43.83 ± 22.09	0.19388
Role limitations-emotional	11.00 ± 17.04	16.66 ± 40.82	0.78815
Mental health	34.66 ± 16.90	44.00 ± 23.32	0.57287
HRSD-21	17.66 ± 4.54	4.83 ± 0.98	0.00052
PLT (mm^3)	108000.0 ± 28748.91	111200.0 ± 30849.64	0.49535
Hb (g/dl)	14.68 ± 0.83	14.14 ± 1.96	0.47785

in haemoglobin levels (12.98 ± 1.40 g/dl *vs.* 12.39 ± 1.77 g/dl).

Conclusions

This study, despite small sample size, indicates that antiviral treatment, combining pegylated interferon alfa 2b and ribavirin, is associated with depression, hence negatively affecting health-related quality of life, not only limited to its mental components, but also extending to its physical ones (Table I). The effect on HRQL appears to occur early during treatment and, although haematological abnormalities and depression are associated with this impairment, depression seems to be the most consistent predictor (Table II). This

TABLE VI.
Changes in HRQL, HRSD-21 scores and haematological parameters; comparison between T1 and T2 in Group 2 (repeated measures ANOVA). *Confronto tra T1 e T2 delle modificazioni dei punteggi della HRQL e della HRSD-21 e dei parametri ematologici nel gruppo 2 (ANOVA per misure ripetute).*

	T1 (mean ± SD)	T2 (mean ± SD)	p
Physical function	74.09 ± 21.58	70.22 ± 26.83	0.18067
Role limitations-physical	44.31 ± 43.59	44.31 ± 46.88	1
Bodily pain	51.31 ± 21. 11	54.90 ± 25.05	0.21458
General health perceptions	48.77 ± 9.85	51.59 ± 9.83	0.22855
Vitality	51.36 ± 17.33	51.81 ± 19.61	0.83864
Social functioning	65.00 ± 22.98	67.86 ± 24.28	0.53828
Role limitations-emotional	53.09 ± 42.03	48.54 ± 44.55	0.37977
Mental health	59.40 ± 13.95	57.95 ± 20.62	0.55880
HRSD-21	8.18 ± 4.13	7.09 ± 3.55	0.59873
PLT (mm^3)	146550.0 ± 58260.28	135550.0 ± 56223.68	0.07785
Hb (g/dl)	12.98 ± 1.40	12.39 ± 1.77	0.01750

observation seems to be supported by the finding of higher haemoglobin levels in patients with diagnosis of major depressive disorder than in patients without depression during antiviral therapy. As reported in other studies HRQL and depression, this is not generally associated with age, antiviral therapy, history of substance abuse or previous antiviral treatment (Table IV). Finally the use of antidepressants reduces depressive and physical symptoms, and improves health-related quality of life. In summary, our data emphasize the importance of investigating the physical and psychological experiences and HRQL of patients with chronic hepatitis C during antiviral treatment. Future studies are needed to evaluate specific personality traits or other biological parameters that could be associated with psychiatric side effects of antiviral therapy and the effect of antidepressant treatment in a larger sample.

References

1 Manns MP, McHutchinson JG, Gordon SC et al. *Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomized trial*. Lancet 2001;358:958-65.

2 Dan AA, Martin LM, Crone C, Ong JP, Farmer DW, Wise T, et al. *Depression, anemia and health-related quality of life in chonic hepatitis C*. J Hepatol 2006;44:491-8.

3 Horsmans Y. *Interferon-induced depression in chronic hepatitis C*. J Antimicrob Chemother 2006;58:711-3.

4 Raison CL, Demetrashvili M, Capuron L, Miller AH. *Neuropsychiatric adverse effects of interferon-alpha: recognition and management*. CNS Drugs 2005;19:105-23.

5 Bernstein D, Kleinman L, Barker CM, Revicki DA, Green J. *Relationship of health-related quality of life to treatment adherence and sustained response in chronic hepatitis C patients*. Hepatology 2002;35:704-8.

6 Kraus MR, Scha¨fer A, Csef H, Faller H, Mork H, Scheurlen M. *Compliance with therapy in patients with chronic hepatitis C. Associations with psychiatric symptoms, interpersonal problems, and mode of acquisition*. Dig Dis Sci 2001;46:2060-5.

7 Schaefer M, Engelbrecht MA, Gut O, Fiebich BL, Bauer J, Schmidt F, et al. *Interferon alpha (IFNalpha) and psychiatric syndromes: a review*. Prog Neuropsychopharmacol Biol Psychiatry 2002;26:731-46.

8 Valentine AD, Meyers CA, Kling MA, Richelson E, Hauser P. *Mood and cognitive side effects of interferon-alpha therapy*. Semin Oncol 1998;25:39-47.

9 Schäfer A, Scheurlen M, Seufert J, Keicher C, Weißbrich B, Rieger P, Kraus MR. *Platelet serotonin (5-HT) levels in interferon-treated patients with hepatitis C and its possible association with interferon-induced depression*. J Hepatol 2009 Oct 21 [Epub ahead of print].

10 Schaefer M, Schwaiger M, Garkisch AS, Pich M, Hinzpeter A, Uebelhack R, et al. *Prevention of interferon-alpha associated depression in psychiatric risk patients with chronic hepatitis C*. J Hepatol 2005;44:793-8.

11 Sockalingam S, Abbey SE. *Managing depression during hepatitis C treatment*. Can J Psychiatry 2009;54:614-25.

12 Capuron L, Gumnick JF, Musselman DL, et al. *Neurobehavioral effects of interferon-α in cancer patients; phenomenology and paroxetine responsiveness of symptom dimensions*. Neuropsychopharmacology 2002;26:643-52.

13 Raison CL, Borisov AS, Broadwell SD, Capuron L, Woolwine BJ, Jacobson IM, et al. *Depression during pegylated interferon-alpha plus ribavirin therapy: prevalence and prediction*. J Clin Psychiatry 2005;66:41-8.

14 Pockros PJ, Shiffman ML, Schiff ER, Sulkowski MS, Younossi Z, Dieterich DT, et al. *Epoetin alfa improves quality of life in anemic HCV-infected patients receiving combination therapy*. Hepatology 2004;40:1450-8.

15 *Diagnostic and Statistical Manual of mental disorders – 4th Edition (DSM-IV)*. American Psychiatric Association (APA) 1994.

16 Hamilton M. *A rating scale for depression*. J Neurol Neurosurg Psychiatry 1960;23:56-62.

17 Ware JE Jr, Sherbourne CD. *The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection*. Med Care 1992;30:473-83.