ORIGINAL RESEARCH

Quality of life, depression, and cytokine patterns in patients with chronic hepatitis C treated with antiviral therapy

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Manuscript submitted 12th February, 2009

Manuscript accepted 12th April, 2009

Clin Invest Med 2009; 32 (3): E212-E218.

Abstract

Purpose: To evaluate the effect of chronic hepatitis C and antiviral therapy on health-related quality of life (HRQoL), depression symptoms and cytokine patterns.

Methods: Twenty HCV+ patients treated with peginterferon plus ribavirin were enrolled in this cohort study and invited to complete SF-12 and BDI questionnaires prior to (T0) and at the end of the treatment (T1). HCV-RNA, serum levels of ALT, AST, haemoglobin, ferritin and IFN- γ , TNF- α , IL-2, IL-4, IL-6 and IL-10 were evaluated at T0 and T1. The questionnaire results were correlated to biochemical and cytokine parameters.

Results: Two patients (1%) dropped out and 18 HCV patients composed the final sample (11 males (61.1%); mean age 42.5 ± 11.9 yr; mean disease duration 9.7 ± 6.9 yr). Between T0 and T1 ALT ($p=0.02$), AST ($p=0.052$) HCV-RNA ($P=0.0002$) and haemoglobin levels decreased ($p=0.0003$), whereas ferritin level increased ($P=0.003$). Also, at T1 all cytokine levels were augmented. Regarding depression status, at T0 10 patients (55.5%) scored above to the BDI questionnaire (suggesting clinically significant depression), whereas at T1 14 patients scored 10 or above (77.7%). At T1 the mean BDI score increased, but this difference was not significant. Regarding HRQoL, the majority of patients had T0 summary scores ≤ 50 . At T1 HRQoL changed and scores decreased in 66.7% of the patients.

A correlation was observed between the T0 level of ferritin and the amount of change in BDI and SF-12 mental score between T0 and T1 (Spearman rho = -0.56 and +0.61, respectively) and IL-4 level at T0 and the change in BDI and SF-12 mental scores (Spearman rho = -0.49 and +0.45, respectively).

Conclusion: BDI, SF-12, IL-4 and ferritin are good tools to predict the appearance of depressive symptoms and worsening of the quality of life in the HCV+ population.

Hepatitis C virus (HCV) infection is the major cause of chronic liver disease worldwide leading 60% up to 80% of patients to develop a chronic infection¹ and is the primary indication for liver transplantation worldwide. This economic burden is multiplied by the dramatic impact of HCV on health related quality of life (HRQoL) resulting from complications of advanced liver disease.² On the other hand, evolving data indicate that HCV itself may diminish HRQoL in the absence of advanced liver disease², perhaps as a result of extrahepatic symptoms related to HCV, cognitive dysfunction related to HCV, or a negative synergy between HCV and comorbid psychosocial disorders.³

Combination therapy with pegylated interferon (Peg-IFN) and ribavirin (RBV) is the standard of care for HCV patients because it induces a higher sustained virological

response.⁴⁻⁵ Indeed, patients treated with Peg-IFN commonly experience a “flu-like syndrome”, fatigue, anxiety and depression. These symptoms negatively affect patient’s functional health, ability to work, self-perceived health, HRQoL and well-being.⁵ Some studies have indicated a possible relationship between depressive symptoms and long-term IFN therapy.⁶⁻⁷

There is some evidence that HCV patients who experience greater fatigue, greater psychiatric symptoms, and poorer HRQoL are more likely to discontinue treatment prematurely with negative impact on virologic response.⁸ Moreover, anti-viral therapy for HCV is associated with diminished HRQoL.⁹

The mechanism by which IFN induces depression remains unclear and is most probably multifactorial.¹⁰⁻¹¹ Several studies suggest that an imbalance between T-helper (Th)1 cytokines and Th2 cytokines or pro-inflammatory and anti-inflammatory cytokines could play a role in the appropriate modulation of cellular responses in the brain during psychological stress and psychiatric disorders.¹²⁻¹⁴ Moreover, the Th1/Th2 cytokine balance is likely to be important for determining the rate of HCV infection chronicity and HCV-induced liver injury¹⁵⁻¹⁷ and could affect the response to IFN therapy.¹⁸

In this study we evaluated HRQoL and depression symptoms in a cohort of patients with active chronic hepatitis C before and after treatment with Peg-IFN (α -2a e α -2b) and ribavirin the role of cytokine patterns with the onset of psychiatric symptoms.

Materials and Methods

The cohort study protocol was approved by the Local Ethical Committee and a written informed consent was obtained by all participants.

Between March and August 2006, 54 consecutive ambulatory adult caucasian patients affected by

chronic hepatitis C (CHC) that were initiated to peginterferon plus ribavirin therapy, based upon current clinical guidelines¹⁹, were asked to participate in the study. Patients were included if they had serologically proven HCV infection, quantifiable HCV RNA detected by Polymerase Chain Reaction (PCR) and persistently elevated serum. A total of 34 were deemed ineligible. Exclusion criteria were evidence of hepatic decompensation (variceal bleeding, ascites, encephalopathy; n=5), other liver disorders (hemochromatosis, genetic liver disease, auto-immune disease; n=3); serious medical disorders that would preclude treatment with interferon (n=4); interferon intolerance prior treatment (n=7); active use of illicit drugs (n=6); active alcohol abuse (n=4); history of a severe or uncontrolled psychiatric condition within the past 6 months (n=2) and refusal to provide informed consent (n=3). We also excluded subjects with current mood disorders and/or antidepressant therapy and those who had previously been treated with IFN.

The remaining 20 patients were enrolled in the study and were treated with peginterferon plus ribavirin. Peginterferon α -2a was administered as a once-weekly subcutaneous injection of 180 μ g, peginterferon α -2b as a once-weekly subcutaneous injection of 1.5 μ g/Kg; ribavirin was given orally at a dose of 800-1200 mg per day administered in two split doses. Data on biochemical parameters, HRQoL and depression status were evaluated at the start (T0) and at the end of the therapy (T1).

Biochemical parameters

Fasting blood samples were taken at T0 and T1 in sterile heparinized tubes, transported on ice to the laboratory, centrifuged at 6 °C and the serum was kept frozen at -70 °C until assayed. Overall, the following parameter blood levels were measured: alanine aminotransferases (ALT), aspartate aminotransferases (AST), haemoglobin, ferritin, and selected cytokines (IFN- γ , TNF- α , IL-2, IL-4, IL-6 e IL-10).

HCV infection was diagnosed using positive HCV antibody test, detectable serum HCV-RNA and persistently elevated ALT and AST levels. HCV antibody was evaluated by a third-generation recombinant immunoblot assay (RIBA 3.0; Ortho Diagnostics, Emeryville, CA, USA). Serum HCV-RNA was determined by PCR (Amplicor method - Roche Mol. Diagn., Milan, Italy), with detection limit of 600 UI/mL.

IFN- γ , TNF- α , IL-2, IL-4, IL-6 and IL-10 were evaluated by Cytometric Bead Array Assay (Human Th1/Th2 Cytokine kit, BD Biosciences, San Diego, CA). For this assay, soluble cytokines are captured on microparticles and then measured using a fluorescence-based detection system and flow cytometry analysis as previously described.²⁰ A series of 10 dilutions from cytokine standards were run in each assay for the generation of standard curves. Sample were analyzed in a FACSCalibur flow cytometer using the BD CBA Analysis Software which, for each cytokine, provides the mean value for statistical analysis.

Health-Related Quality of Life

The self-administered version of the Short-Form (SF-12) health survey questionnaire was used to evaluate HRQoL.²¹ The SF-12 is a validated subset of questions contained in the SF-36, and evaluates the same domains as the SF-36. The SF-12 is a widely used instrument and has shown good internal consistency and reliability.²² Two summary scores, evaluating different domains, can be derived from the SF-12: the Mental Component Summary (MCS) and Physical Component Summary (PCS). Both scores range between 0 and 100, with an usual median at 50 [21]. The HRQoL instrument was self-administered by patients at T0 and T1.

Depression

Depression was evaluated at baseline using the Beck Depression Inventory (BDI), a 21-item self-reported measure most widely used depression scale. The items for the BDI cover emotional, behavioural and somatic

symptoms.²³ The BDI was self-administered by patients at T0 and T1. Scores range from 0 to 63: a score ≥ 10 is considered a valid indication of clinically significant depression. Complete depression scoring was available for 100% of the cohort.

Data analysis

The normality distribution of all continuous variables investigated was examined using the Shapiro-Wilk test and, in case of non-normal distribution, results were expressed as median and interquartile range. The level of these variables before and after the therapy were compared using paired t-test or Wilcoxon matched-pairs rank sum test, depending on their distribution. Changes in categorical variables were tested using Mc Nemar's statistics, and multiple regression analysis was used to evaluate potential independent predictors of BDI, SF-12 physical and mental summary score changes. Skewed covariates were log transformed, dichotomized or categorized into percentiles when appropriate. Quadratic and interaction terms were tested for all significant variables included in the model, whose validity was assessed by means of usual diagnostic tools (residual, outlier and multicollinearity analyses). Statistical significance was defined as a two-sided *P*-value < 0.05 for all analyses, which were carried out using STATA statistical software, version 8.2 (Stata Corp., College Station, Texas, USA).

Results

Of the 20 patients that accepted to participate in the study, two (1%) did not complete the cycle of treatment because of severe adverse effects (pancytopenia) and were thus dropped from the analysis. The general characteristics of the 18 HCV patients composing the final sample are reported in Table 1. Eleven patients were males (61.1%); the mean age was 42.5 ± 11.9 yr, and the mean disease duration was 9.7 ± 6.9 yr.

Between the beginning and the end of the therapy (T0 and T1), all indices of liver function showed im-

TABLE 1. General characteristics of the 18 patients with HCV related hepatitis.

Variables	% (n)
Male, %	61.1
Age, y	42.5 ± 11.9
Disease duration, y	9.7 ± 6.9
<i>Therapy</i>	
IFN α -2a, %	44.4
IFN α -2b, %	55.5
<i>Genotypes, %</i>	
1a	22.2
1b	27.7
2a	16.6
2c	16.6
3a	16.6

provement: ALT ($P=0.02$), HCV-RNA ($p=0.0002$), and haemoglobin levels decreased, ($p=0.0003$) whereas ferritin level increased ($P=0.003$); reduction of AST was not significant (Table 2). Also, after the treatment all cytokine levels were augmented.

As regards depression status, at the start of the study, 10 patients (55.5%) scored above to the BDI questionnaire (suggesting clinically significant depression), whereas at the end of the therapy 14 patients scored 10 or above (77.7%). As shown in Table 3, after treatment the mean BDI score increased, but this difference was not significant.

Regarding HRQoL, all patients completed every question of the SF-12 in both surveys (at time 0 and after therapy), and the majority of patients had baseline physical and mental summary scores ≤ 50 , which represents the average summary score in the US population²⁴ (respectively, 66.7% and 61.1%). The changes in HRQoL are shown in Table 3. Compared with baseline, both physical and mental summary mean scales worsened ($P=0.047$ and 0.014 , respectively), and both scores decreased in 66.7% of the patients.

A correlation was observed between the baseline level of ferritin and the amount of change in BDI and SF-12 mental score between baseline and the end of therapy (Spearman $\rho = -0.56$, $P=0.01$ and $\rho = +0.61$, $P=0.007$ respectively). Similarly, the change in

TABLE 2. Indices of liver function and cytokines before and after the antiviral therapy

	T0	T1	<i>P</i>
<i>Liver function indices</i>			
AST (U/L)	42 (23)	30 (13)	0.052
ALT (U/L)	58 (30)	37 (36)	0.028
Ferritin (mcg/L)	123 (77)	247 (380)	0.003
Mean Hemoglobin (mg/dL)	13.9 (1.7)	11.8 (1.6)	0.0003
HCV-RNA ($\times 10^4$) UI/mL	46 (38)	0 (0)	0.0002
<i>Cytokines ($\mu\text{g/L}$)</i>			
IFN- γ	0 (77.7)	123.0 (62.1)	0.001
TNF- α	1.8 (1.9)	5.1 (3.8)	0.006
IL-2	0 (4)	19.4 (24)	0.015
IL-4	0 (2.1)	5.8 (6.6)	0.001
IL-6	7 (4.3)	26.6 (18.8)	0.0007
IL-10	0 (0)	4.9 (6.3)	0.0003

When not differently stated, data are expressed as median (inter-quartile range).

BDI and SF-12 mental scores was correlated with interleukin-4 level at baseline (Spearman $\rho = -0.49$, $P=0.03$ and $\rho = +0.45$, $P=0.05$, respectively). Finally, and expectedly, BDI and SF-12 mental score changes were strongly and negatively correlated (Spearman $\rho = -0.77$; $P<0.001$).

Discussion

Our data confirm that patients affected by CHC ongoing therapy with Peg-IFN and ribavirin can have an improvement of liver function in terms of virological and biochemical response at the end of the treatment but can develop side effects as anemia.²⁵⁻²⁶ Ribavirin-induced anemia is one important determinant of HRQoL during antiviral-therapy for HCV that nega-

TABLE 3. Beck Depression Inventory (BDI) and SF-12 physical (PCS) and mental (MCS) summary scores before and after treatment.

	T0	T1	<i>P</i>
BDI	16.3 ± 11.7	22.5 ± 11.0	0.12
PCS	47.8 ± 6.6	41.2 ± 12.9	0.047
MCS	48.4 ± 8.1	40.4 ± 10.3	0.014

tively affected disease-specific and generic aspect of HRQoL.²⁷ In our data the occurrence of an increase of ferritin is also common, as widely reported in literature.²⁸⁻²⁹

Analysis of the questionnaires administered before and at the end of the antiviral treatment has shown that our patients experienced worsening of the HRQoL stated by both depressive indexes and by the health physical and mental status. These findings are reported by the decrease of the SF-12 parameters in comparison to the baseline. Considering the SF-12 score, we found that MCS change is negatively correlated to BDI change, and both are related to an increase of the level of depression.

Moreover, in our study we have analysed cytokine patterns during the antiviral therapy and the possible correlation with the quality of life and depression. Our results have shown an increase between T0 and T1 of all the cytokine Th1 and Th2 we analysed. Because the patients showed increase of the level of depression at the end of antiviral treatment, these findings that the Th1 and Th2 cytokine levels were higher at T1 are in agreement with previous reported findings.¹¹ In particular, at the end of the therapy we have observed an increase of all anti-inflammatory cytokines (IL-2, IL-4 and IL-10) and of the pro-inflammatory cytokine IFN- γ . We suggest that this result might be due to a positive effect on the inflammatory status of the chronic hepatitis of the anti-HCV therapy. The determination of the serum levels of the monocytic pro-inflammatory cytokines IL-6 and TNF- α has been higher at the end of the administration of the therapy versus the beginning. Previous studies showed that pro-inflammatory cytokines such as IL-1 β , IL-6 and TNF- α , elicited sickness behaviours (e.g., fatigue, soporific effects) and symptoms of anxiety/depression and rise quickly in response to stress stimuli.³⁰ Recent studies have also demonstrated the possible causative role of IL-6 in the development of depression [31], the IL-6 positive correlation with the severity of depressive symptoms and association with psychotic

symptoms.¹⁴ So, we suppose that our results might be related to the adverse effects of the antiviral therapy.

By the analysis of our data, we found that treatment with Peg-IFN and ribavirin is associated with worsening of the quality of life in terms of mental and physical conditions as we expected and reported in literature.³²⁻³⁴ Measurement of the quality of life and the screening for mood disorders before and during the therapy is thought to be of extreme importance. In our experience, self-administered questionnaires are suitable to assess psychiatric and other adverse events among chronic patients on therapy, as reported in literature in other medical settings.³⁵⁻³⁶

The impact of Peg-IFN and ribavirin on the cytokine patterns is not completely clear.¹⁶⁻¹⁸ In the literature some authors have suggested that some cytokines (eg. some interleukins) activated by IFN- α can play a role in the induction of depressive symptoms involving the serotonergic system, hypothalamic-pituitary-thyroid axis, and the cytokine network.³⁷⁻³⁸

The relationship between ferritin and depression has rarely been studied.³⁹ Some reports indicated that chronic hemodialysis patients with major depression had higher ferritin levels.⁴⁰ Many reports show that depression is accompanied by activation of the immune/inflammatory system, including an acute phase response.⁴¹ So serum ferritin levels might be related to an acute-phase reaction.⁴²⁻⁴³

There is no data showing a correlation between depression indexes by BDI, indexes of the quality of life by SF-12 and levels of ferritin in HCV infected patients. Interestingly, we found a correlation between BDI and SF-12 change with IL-4 and ferritin. The increase of the levels of ferritin and of IL-4 value at the baseline are strongly associated with the decrease of BDI change and with the increase of the MCS change. BDI and MCS change are considered parameters of an evolution towards a major depression and of a worsening of the mental health status of HCV+ patients on treatment. So, if confirmed by further studies the determination of serum IL-4 and ferritin before and during the administration of the antiviral therapy might

be important for its correlation with BDI and SF-12 change.

However, there were many factors that might have confounded our results, including age, duration of antiviral therapy, and small sample size. Additionally, since we collected the plasma samples only in the beginning and at the end of peginterferon plus ribavirin therapy, some changes in cytokine levels and biochemical parameters could have missed. So, it is hard to say whether the IL-4 and ferritin are really predictive of depression or appear at the same time as depression. Moreover, if we also measured the cytokine levels in basal and stimulated whole blood culture supernatants, we might have obtained a more comprehensive view regarding the changes. Future studies will attempt to assess these possibilities.

In conclusion our results indicate that self-administered questionnaires, cytokine evaluation and ferritin might be used to detect depressive symptoms and possible alterations in the quality of life of HCV positive patients during antiviral treatment. Further studies are needed to confirm these results that may help the physician to understand and give a better support to patients with chronic hepatitis C.

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