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The Effect of Early Virological Response in Health-Related Quality of Life in HCV-Infected Patients

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Twenty-nine HCV-infected patients were treated with pegylated interferon alpha. Diagnosis was based on serum HCV RNA-PCR positive results and liver biopsy. All patients had elevated serum levels of alanine aminotransferase at the time of the study, but liver disease was compensated. Patients were evaluated at baseline treatment and after 4 and 12 weeks of antiviral treatment with the Medical Outcomes Study 36-item Short-Form Health Survey. The Mini-International Neuropsychiatric Interview was used to exclude previous or current psychiatric diagnoses. Both patients and psychiatrists were blind to the HCV RNA status, and serum HCV RNA test results only became available after the visit at week 12. After antiviral treatment, 16 patients (55.2%) were classified as nonresponders and 13 (44.8%) were classified as responders. When compared to nonresponders, responders had a greater improvement in the HRQOL scores for the mental health domain ($P < .019$). Differences in other domains were not significant. The present study confirms that active viral infection is one possible reason for the poor Health-Related Quality of Life in this population. ***J. Med. Virol. 80:419–423, 2008.***

KEY WORDS: hepatitis C; interferon alpha; quality of life; depression

INTRODUCTION

Hepatitis C virus (HCV) infection, even when apparently asymptomatic, is often associated with neurological damage. There is growing evidence that chronic infection with HCV (family *Flaviviridae*, genus *Hepacivirus*, species *Hepatitis C virus*) is not an asymptomatic disease, and there is more recent evidence concerning its neuroinvasion [Laskus et al., 2000; Forton et al., 2005]. HCV-infected individuals, even in the absence of clinically significant liver disease, often complain of "brain fog," characterized by fatigue, depression, forgetfulness, and difficulty in concentrating [McAndrews et al., 2005].

In addition, large studies evaluating extra-hepatic manifestations in patients with chronic hepatitis C have consistently found a significant reduction in the health-related quality of life (HRQOL) [Bonkovsky et al., 1999; Ware et al., 1999]. Interestingly, this reduction in the HRQOL measures should be independent of the severity of liver impairment and are observed in different quality of life domains. Foster et al. [1998] found that the HRQOL scores were lower in patients with HCV infection when compared with both healthy controls and patients with chronic hepatitis B virus (HBV) infection, suggesting that there is a specific C virus cerebral effect. Poor HRQOL scores were not related to the mode of HCV acquisition and neither to the presence of previous intravenous drug use. Taking these findings together and considering that different cohort studies have shown significant improvements in HRQOL after successful antiviral therapy, it is reasonable to infer that the viral infection itself is an important determinant of reduced HRQOL [Bonkovsky et al., 1999; Ware et al., 1999; McHutchison et al., 2001].

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However, the possible role of distress associated with a chronic disease diagnosis, which may influence HRQOL negatively [Rodger et al., 1999; Hauser et al., 2004], could not be ruled out. Most studies examining HRQOL in HCV-infected subjects had both patients and clinicians aware of the serological status, which appears to be a major methodological limitation [Rodger et al., 1999]. In this sense, an improvement in HRQOL after successful antiviral therapy may be at least attributed in part to the patients knowledge of the response to treatment [Forton et al., 2005].

In order to investigate whether the viral C eradication is per se related to quality of life improvement according to HRQOL, a prospective study to evaluate changes in quality of life during treatment with pegylated interferon (peginterferon) plus ribavirin was performed. Patients and clinicians were blind to the serological status during the study. Bearing in mind findings from previous studies, it was hypothesized that treatment-responding individuals would have more prominent improvement in HRQOL measures after treatment compared with those not responding.

METHODS

Patients

Patients were recruited from the Northeastern region of Brazil, before peginterferon/ribavirin treatment. The study was approved by the Medical Review Ethics Committee of the Federal University of Bahia, Brazil. All patients provided written informed consent. Twenty-nine patients volunteered to participate and completed psychiatric evaluations during treatment. Patients were treated at an academic medical center (Gastro-Hepatology Unit, Federal University of Bahia, Medical School). Twenty-three patients received peginterferon alpha-2b 1.5 mcg/kg/week plus ribavirin 1.200 mg/day and six received peginterferon alpha-2a 180 μg/week plus ribavirin 1.200 mg/day. Diagnosis confirmation was based on serum HCV RNA-PCR positivism and liver biopsy. All patients had elevated serum levels of alanine aminotransferase at the time of the study, but liver disease was compensated. Exclusion criteria included current pregnancy, history of current psychiatric disorders according to the Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition (DSM IV) criteria, history of substance abuse in the last 6 months, presence of other liver diseases, autoimmune disease, serious or unstable cardiovascular, renal, respiratory, or hematological illness, or any other medical condition that could compromise participation or lead to hospitalization during the study.

Procedures

Neither the patients nor the psychiatrists knew the HCV RNA status, and serum HCV RNA test results only became available after the visit at week 12. An initial virological response was defined as undetectable plasma HCV RNA at week 12 of treatment.

Patients were evaluated at baseline and after 4 and 12 weeks of peginterferon treatment. The Medical Outcomes Study 36-item Short-Form Health Survey (SF-36) [Ware et al., 1993], translated and validated for use in Portuguese [Ciconelli, 1997], was performed at each assessment.

The self-administered version of the Short Form (SF)-36 Health Survey was included to measure comprehensively HRQOL [Obhrai et al., 2001; McDonald et al., 2002]. The SF-36 is a generic health status measure that consists of 36 items and eight domains: physical components (1, physical function; 2, role limitations—physical; 3, general health perceptions; and 4 pain) and mental components (5, vitality; 6, social function; 7, role limitations-emotional; and 8, mental health) [McDonald et al., 2002]. Domain scores were linearly transformed into a 0 (worst health) to 100 (best health) scale. A profile of functional health and well-being scores as well as psychometrically based physical and mental health summary measures were also generated [Obhrai et al., 2001]. The SF-36 has demonstrated good reliability and validity in chronic disease populations, including patients with chronic hepatitis C [Ware et al., 1994a; Jamal et al., 1999; Forton et al., 2002].

Patients were evaluated at baseline treatment with the Mini-International Neuropsychiatric Interview (MINI); a short, structured diagnostic psychiatric interview for axis I DSM-IV disorders, to exclude previous or current psychiatric diagnoses. The MINI contains 130 questions and screens 16 axis I DSM-IV disorders and one personality disorder. Excellent interrater and test–retest reliabilities of the English version of MINI, and moderate validity of MINI versus other structured diagnostic psychiatric interviews were reported. It was validated to Portuguese by Amorim [2000] with good reliability and validity.

Statistical Analyses

Data were recorded and analyzed using the Statistical Package for Social Sciences (SPSS for Windows, version 9.0). All analyses were two-tailed and alpha level was set at P values <0.05. Proportion differences were compared using either the chi-square test or Fisher's exact test, where appropriate. Continuous variables were compared by using Student's t-test or Mann–Whitney test for nonparametric data. Because of the exploratory character of the study, we did not correct P values nor calculate the sample size.

RESULTS

Doses of interferon were not reduced during the study. Only one patient interrupted the treatment before week 12. Baseline sociodemographic and clinical characteristics of patients are summarized in Table I.

Three patients (10.3%) had past history of psychiatric treatment for intravenous drug use and one (3.4%) for alcohol dependence. Two patients (6.9%) had also met criteria for past cannabis abuse and two for alcohol

TABLE I. Baseline Characteristics of 29 Study Patients

Characteristics	CHC patients
Age at beginning of PEG IFN thearapy mean (±SD)	49.02 ± 7.69
Gender	
Male, N (%)	24 (82.75)
Female, N (%)	5 (17.25)
Weight (Kg ± SD)	76.12 ± 11.6
Genotype	
1, N (%)	21 (72.4)
3, N (%)	8 (27.6)
Peg IFN alpha-2a, N (%)	6 (20.7)
Peg IFN alpha-2b, N (%)	23 (79.3)
Cirrhotic, N (%)	15 (51.72)
Risk factor for HCV	
Unknown, N (%)	12 (41.37)
IVDU, N (%)	3 (10.34)
Transfusion, N (%)	8 (27.58)
Contaminated instruments, N (%)	5 (17.25)
Tattoo, N (%)	1 (3.44)

PEG IFN, pegylated interferon; HCV, Hepatitis C virus; IVDU, intravenous drug use; N, number; SD, standard deviation.

abuse (one is the same subject who had a current diagnosis of substance abuse).

After treatment with peginterferon/ribavirin, 16 patients (55.2%) were classified as nonresponders and thirteen (44.8%) were classified as responders.

When compared to nonresponders, responders had a greater improvement in HRQOL scores for the mental health domain ($P < 0.019$). Differences in other domains were not significant (Table II).

DISCUSSION

The present results suggest that the initial virus eradication, during peginterferon/ribavirin, is associated with significant improvement in patient mental health, as measured by SF-36.

In contrast, previous reports suggest that interferon therapy negatively affects HRQOL of patients with chronic hepatitis C during the initial 12–24 weeks of treatment and is associated with several psychiatric and neurological side effects [Neary et al., 1999; Quarantini et al., 2006a, 2006b, 2007].

TABLE II. Baseline to 12-Week Mean Changes in HRQOL for Virologic Responders and Nonresponders

	Virologic responders	Virologic nonresponders	
SF-36 subscale	Mean (SE)	Mean (SE)	*P*
Mental health			
Baseline	72.5 (5.95)	82.15 (3.67)	0.30
Week 4	81.07 (4.05)	76.23 (3.96)	0.25
Week 12	80.80 (4.17)	63.38 (6.09)	0.019*
Role-emotional			
Baseline	79.84 (11.02)	95.88 (2.82)	0.55
Week 4	64.1 (13.32)	86.69 (7.83)	0.31
Week 12	89.77 (7.9)	86.87 (9.09)	0.96
Physical functioning			
Baseline	85.94 (5.11)	86.56 (4.2)	0.88
Week 4	85.77 (5.12)	88.67 (4.96)	0.52
Week 12	84.23 (4.8)	82.33 (5.95)	0.981
Role-physical			
Baseline	87.69 (5.95)	82.81 (8.45)	0.77
Week 4	55.77 (13.02)	65 (10.86)	0.71
Week 12	60 (11.21)	63.33 (10.87)	0.71
Bodily pain			
Baseline	82.31 (5.1)	80.84 (4.97)	0.84
Week 4	73.23 (5.82)	68.87 (4.82)	0.71
Week 12	76.35 (5.55)	75.90 (4.87)	0.92
General health			
Baseline	79.52 (3.40)	72.81 (5.2)	0.77
Week 4	80 (4.04)	77 (4.52)	0.78
Week 12	77.08 (3.95)	77 (3.71)	0.98
Vitality			
Baseline	74.23 (3.96)	69.06 (5.74)	0.77
Week 4	68.46 (4.36)	70 (4.45)	0.68
Week 12	56.92 (6.11)	60.77 (5.64)	0.78
Social functioning			
Baseline	84.69 (5.33)	90.03 (4.23)	0.37
Week 4	80.15 (6.73)	87.83 (3.79)	0.52
Week 12	71.19 (8.75)	90.07 (4.07)	0.18

PEG IFN, pegylated interferon; HRQOL, health-related quality of life; results expressed as mean; SE, standard error.
*$P < 0.05$.

Importantly, the present results were not influenced by the patients or the clinician knowledge of the response to treatment, since both were blind to the HCV polymerase chain reaction status. Additionally, other relevant determinants of HRQOL impairment such as medical and mood disorder comorbidities [Rodger et al., 1999; Dwight et al., 2000; Fontana et al., 2002] were excluded from this sample. Patients with either a previous or current mood disorder episode were excluded.

Among the SF-36 sub-scales, mental health domain has been shown to be the most valid measure of mental health in different studies [McHorney et al., 1993; Ware et al., 1993; Ware et al., 1994b].

Most of the previous reports indicated an association between HRQOL and sustained virological response, but with the limitation that the patients had been informed of their HCV RNA status at intervals during the trials [Bernstein et al., 2002]. Rodger et al. [1999] reported that individuals who knew they were infected actively with HCV had lower HRQOL scores than subjects who were unaware of their serostatus.

Teixeira et al. [2006] study found improvement of HRQOL after viral eradication when patients and raters were blind to their serostatus, concluding that a more comprehensive improvement in HRQOL domains, and mental health improvement could be a consequence of other physical health improvements. The present findings are in agreement with Teixeira et al. [2006], but with the conclusion that just the effective viral eradication treatment is enough to explain the mental health improvement.

Despite the small sample size, it was still large enough in order to detect differences in the mental health domain of HRQOL, but not so large as to find differences in other domains. In addition, one might not be able to generalize these findings to groups of patients with hepatitis C who are intravenous drug users or who present an affective disorder.

In conclusion, the results provide information on a possible association between improvement of HRQOL and successful antiviral treatment of HCV-infected patients. It suggests that active viral infection is one possible reason for poor HRQOL in this population. However, the pathophysiological mechanisms underlying this relationship remain unclear. It is necessary to perform further longitudinal studies with larger sample sizes, and a longer follow-up on HCV-infected subjects from the asymptomatic stages through the post-treatment remission stages.

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