Notice of Correction: The institutional affiliation of Mr. Castellvi and Dr. Subirà was omitted in the print article. The Universitat Autònoma de Barcelona has been added on page 817.

Pegylated Interferon and Ribavirin–Induced Depression in Chronic Hepatitis C: Role of Personality

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Objective: Pegylated interferon (PegIFN) and ribavirin (RBV) treatment for the hepatitis C virus (HCV) infection can induce depressive episodes. Personality traits have been associated with mood disorders. The aim of this study was to evaluate the personality profile as a risk factor for induced depression by PegIFN and RBV treatment in patients with HCV.

Method: In a prospective cohort study, 204 consecutive HCV outpatients who received PegIFN and RBV were assessed using the Structured Clinical Interview for DSM-IV Axis I Disorders and the Temperament and Character Inventory-Revised (TCI-R). Moreover, the Patient Health Questionnaire and the Hospital Anxiety and Depression Scale were administered at baseline and at 4, 12, 24, and/or 48 weeks of treatment. Patients were recruited between September 2003 and December 2006.

Results: One hundred eighteen patients (57.8%) were men. The mean (SD) age was 44.39 (10.4) years. The incidence of induced depression during the 48 weeks of antiviral treatment was 73 (42%). Low self-directedness dimension (HR = 0.63, 95% CI = 0.446 to 0.890, p = .009), baseline subclinical depression levels (HR = 1.113, 95% CI = 1.023 to 1.22, p = .013), and history of mood disorders (HR = 0.372, 95% CI = 0.220 to 0.629, p < .001) were independent predictive factors for induced depression during PegIFN and RBV treatment. Other predictive personality TCI-R subscales were enlightened second nature (HR = 2.939, 95% CI = 1.423 to 6.071, p = .004), fatigability (HR = 0.421, 95% CI = 0.237 to 0.749, p = .01), and disorderliness (HR = 0.449, 95% CI = 0.248 to 0.815, p = .008).

Conclusion: Low self-directedness, depressive symptoms at baseline, and history of previous mood disorders may predict induced depression by PegIFN and RBV in euthymic HCV patients.

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Chronic hepatitis C virus (HCV) infection is a public health problem that affects 3% of the world population.[1,2] Between 20% and 30% of patients develop liver cirrhosis after 15 to 25 years.[3,4] The current recommended treatment for HCV infection is pegylated interferon (PegIFN) and ribavirin (RBV).[5] The duration of PegIFN and RBV treatment (24 or 48 weeks) depends on the HCV genotype, viral response, and development of adverse effects.[5] Sustained virological response (undetectable HCV-ribonucleic acid 24 weeks after the end of treatment) is achieved in 40% to 80% of treated patients depending on the HCV genotype.[6] However, the treatment has been associated with high rates of neuropsychiatric side effects, especially depressive symptoms. These neuropsychiatric adverse events can contribute to impairment in the patient's quality of life[7] and can diminish adherence to antiviral treatment,[8] limiting the efficacy of the treatment.

Some risk factors of IFN-induced depression have been identified before starting antiviral treatment. Subclinical depression or anxiety levels at baseline are the most well-known risk factors.[9–12] Other predictive vari-

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ables are a history of psychiatric disorders,[13] age,[14] sex,[13,15] and social support.[16] However, personality traits have been poorly studied as a risk factor for IFN-induced depression.[17–19]

Personality traits may be associated with the risk of developing affective disorders. Neuroticism, harm avoidance, and low self-directedness have been found to be associated with the risk of developing unipolar depression in both cross-sectional and prospective studies.[20,21] Genetic risk factors for neuroticism, harm avoidance, and depression are related and may interact with other risk factors of affective disorders.[22,23] As far as we know, 3 studies have evaluated personality traits in patients with HCV treated with IFN.[17–19] All of these studies were done in small samples and in a follow-up period of only 12 to 24 weeks of treatment.

Otsubo et al.[17] found that higher neuroticism (Eysenck Personality Questionnaire, EPQ) at baseline was a risk factor for IFN-induced depression in a sample of 83 HCV patients treated for 24 weeks. Malyszczak et al.[18] found that ratings of neuroticism (EPQ) highly influenced all depressive ratings in 44 HCV patients treated with PegIFN-α-2a plus RBV during 12 weeks. Finally, Lotrich et al.[19] observed that high neuroticism in combination with low agreeableness on the Neuroticism, Extraversion, Openness-Five Factor Inventory was a predictor of induced depression by PegIFN plus RBV in 23 euthymic patients at 12 weeks of treatment.

The main objective of this study was to analyze the personality traits of the Temperament and Character Inventory-Revised (TCI-R) according to the model of Cloninger et al.[24–26] as a risk factor for induced depressive disorder during PegIFN and RBV treatment in a large group of HCV-infected patients followed during the entire treatment period. A secondary objective was to analyze if the personality profile of induced-depressed patients was different in patients with depression at baseline.

METHOD

Selection and Description of Participants

All consecutive outpatients with chronic HCV attending the Hepatology Unit of a teaching general hospital in Barcelona, Spain, between September 2003 and December 2006 who were candidates to receive combined treatment with PegIFN and RBV were included in the study. The study protocol was approved by the institutional review board, and all participants signed the written informed consent. The exclusion criteria were as follows: language or cognitive difficulties, presence of other liver disease, decompensated cirrhosis, severe cardiac or neurologic disease, coinfection with hepatitis B, hepatocellular carcinoma, autoimmune disorders, a hemoglobin level < 12 g/dL in men and < 11 g/dL in women, a neutrophil count $< 1.5 \times 10^9$/L, and a platelet count $< 75 \times 10^9$/L. In addition, patients whose baseline evaluation showed the presence of major psychiatric disorders 24 weeks before starting treatment, drug or alcohol abuse, or substance-induced psychotic disorder were also excluded.

Study Design

This was a prospective cohort study. All participants were interviewed at baseline using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I),[27] and they also completed the Patient Health Questionnaire (PHQ),[28] the Hospital Anxiety and Depression Scale-Depression (HADS-D) and -Anxiety (HADS-A),[29] and the TCI-R.[24–26] Patients were also evaluated at 4, 12, 24, and/or 48 weeks of treatment with the PHQ and the HADS. After baseline assessments, patients were given PegIFN-α-2a (180 μg weekly subcutaneously) or PegIFN-α-2b (80 μg weekly subcutaneously) and RBV (600–1200 mg/day orally). The duration of PegIFN and RBV treatment (24 or 48 weeks) depended on the HCV genotype, viral response, and development of adverse effects.[5]

Measurements

We collected at baseline sociodemographic and clinical variables including age, sex, body mass index, immigrant condition, education level, and employment status; human immunodeficiency virus (HIV) coinfection and previous IFN treatment; personal history of alcohol consumption and current methadone treatment; and biologic evaluation: viral load, HCV genotype, and level of liver fibrosis.

All participants were assessed at baseline using the SCID-I in order to ascertain current and past history of psychiatric disorders. If at any point during the study a patient showed clinically relevant depressive symptoms as detected by the PHQ or a HADS-D score of 11 or greater, he or she was referred to an independent senior psychiatrist who confirmed the presence of a depressive disorder diagnosis based on DSM-IV criteria using the depression SCID-I module.

The PHQ is an instrument designed for the screening of depressive and anxiety disorders as well as bulimia nervosa, binge-eating disorder, and alcohol abuse or dependence in primary care and other medical settings. The PHQ allows a current DSM-IV diagnosis of any depressive episode. This screening questionnaire has shown good psychometric properties to detect depression in medical settings. The overall accuracy of the Spanish validated version is 88%, sensitivity is 87%, and specificity is 88%, similar to the original English version. Kappa values of 0.74 were found between PHQ diagnosis and those of an independent mental health professional.[30]

The Spanish version of the HADS[31] is a self-administered questionnaire including 14 items scored on a 4-point Likert scale split into 2 subscales of depression

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and anxiety. This questionnaire was specially designed for the evaluation of anxiety and depression in medical patients.

The TCI-R[26] is a 240-item, 5-point Likert scale, self-report questionnaire measuring 7 personality dimensions. The biopsychosocial model of Cloninger et al.[24] proposed that personality is formed by 4 temperamental and 3 character dimensions.

Temperamental dimensions measure differences in automatic emotional responses to stimuli and define personality style, and they are influenced by different neurotransmitters. Harm avoidance refers to a tendency to shyness, anxiety, pessimism, and anticipatory worry and seems to be associated with serotonin (5-HT) function. Harm avoidance has 4 subscales: anticipatory worry, fear of uncertainty, shyness, and fatigability. Novelty seeking reflects the reward system activity and hence a tendency to impulsiveness, lack of inhibitions, monotony avoidance, and exploratory behavior in response to novelty. It might be involved with mesolimbic and mesofrontal dopaminergic projections. Novelty seeking has 4 subscales: exploratory excitability, impulsiveness, extravagance, and disorderliness.

Reward dependence is associated with conditioned signals of reward; it expresses variation in social bond, affiliation, and dependence on approval of others, putatively linked to norepinephrine function. Reward dependence has 4 subscales: sentimentality, openness to warm communication, attachment, and dependence. Persistence is related to ambitious overachieving and to a tendency to maintain behavior despite frustration, and it could relate with prefrontal activity. Persistence has 4 subscales: eagerness to effort, work hardened, ambitious, and perfectionist.[26]

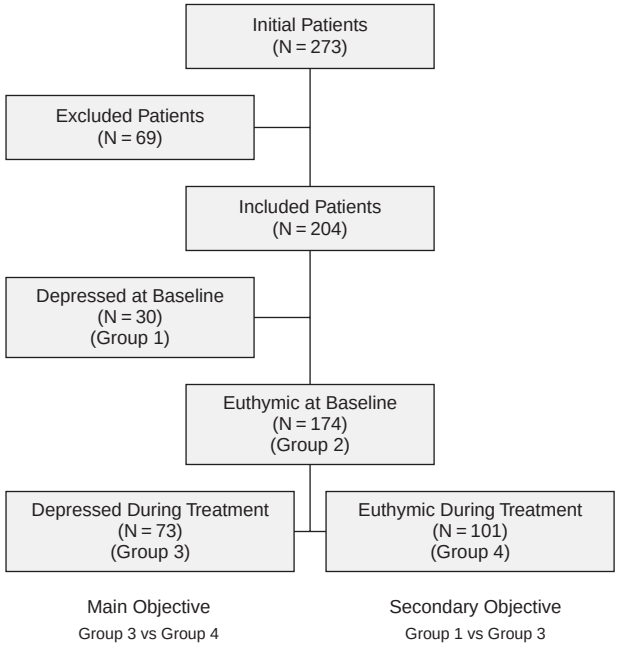
The other 3 dimensions relate to character. Self-directedness reflects the ability to cope effectively and to regulate and adapt behavior in accordance with individual goals and values. Self-directedness has 5 subscales: responsibility, purposefulness, resourcefulness, self-acceptance, and enlightened second nature. Cooperativeness reveals the presence of ethics, social tolerance, and good interpersonal adjustment. Cooperativeness has 5 subscales: social acceptance, empathy, helpfulness, compassion, and pure-hearted consciousness. Finally, self-transcendence is related to imagination, creativity, and religious and magical thought. Self-transcendence has 3 subscales: self-forgetful, transpersonal identification, and spiritual acceptance.[24,25] These traits are determined by environmental factors but might also be influenced by genetic aspects.[32] The Spanish validated version of the TCI-R questionnaire[33] was used in this study.

Statistical Analysis

Data were analyzed using SPSS (version 12.0 for Windows, SPSS, Inc., Chicago, Ill.). We used the absolute and relative frequencies for categorical variables and the mean and standard deviation for continuous variables and Fisher exact test, Student t test, and Spearman's correlation for univariate analysis. Personality scores are presented as t scores. After Bonferroni's correction, statistical significance was set at $p < .017$.

In addition, we studied the time to depression as a dependent outcome. For the univariate analysis, the Kaplan-Meier estimator was applied to estimate the survival curves. All continuous variables were previously categorized for this analysis. In each variable, the log-rank test was used to compare their survival curves. For the multivariate analysis, we assessed the proportional hazards model of Cox. If depression did not occur after 48 weeks of treatment, time to depression was treated as a censored time. Stepwise forward selection was used to determine the final model. We considered statistical significance as $p = .05$.

Figure 1. Organization Chart Showing the Division of the Sample Between Different Groups



RESULTS

Descriptive Analysis

Baseline. From 273 screened patients, 69 (25.3%) did not fulfill the inclusion criteria (Figure 1). Twenty-one patients were not included for medical reasons, 12 patients were participating in other studies, 13 patients refused to participate, 11 patients had a psychiatric non–substance use disorder, and 12 patients had a current substance use disorder (within the last 24 weeks). The

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Table 1. Descriptive and Comparative Analysis Between Groups

Sample Characteristics	Baseline (N = 204)			During Treatment (N = 174)		p[a]
	Total Sample (N = 204)	Depressive (1) (N = 30)	Euthymic (2) (N = 174)	Depressive Induced (3) (N = 73)	Euthymic (4) (N = 101)	1 vs 2 1 vs 3 3 vs 4
Age, mean (SD), y	44.39 (10.4)	44.16 (9.3)	44.43 (10.6)	44.35 (10.6)	44.49 (10.8)	.893 .932 .934
Sex, N (%)						.424
Male	118 (57.8)	15 (50.0)	103 (59.2)	42 (57.5)	61 (60.4)	.519
Female	86 (42.2)	15 (50.0)	71 (40.8)	31 (42.5)	40 (39.6)	.756
Education level, N (%)						.235
Primary	97 (47.5)	18 (60.0)	79 (45.4)	43 (58.9)	35 (34.7)	.559
Secondary	77 (37.9)	10 (33.3)	67 (38.5)	20 (27.4)	48 (47.5)	.007
Higher	30 (14.6)	2 (6.7)	28 (16.1)	10 (13.7)	18 (17.8)	
Employment status, N (%)						.017
Employed/housewife	142 (69.7)	15 (50.0)	127 (73.0)	52 (71.2)	75 (74.3)	.068
Unemployed/retired	62 (30.3)	15 (50.0)	47 (27.0)	21 (28.8)	26 (25.7)	< .001
Immigrant, N (%)	35 (17.2)	6 (20.0)	29 (16.7)	14 (19.2)	15 (14.9)	.610 1.000 .536
HIV positive status, N (%)	54 (26.5)	10 (33.3)	44 (25.3)	24 (32.9)	20 (19.8)	.374 1.000 .054
Genotype, N (%)						.800
1	115 (56.4)	18 (60.0)	97 (55.7)	41 (56.2)	56 (55.4)	.708
2	16 (7.8)	1 (3.3)	15 (8.6)	4 (5.5)	11 (10.9)	.383
3	53 (26.0)	9 (30.0)	44 (25.3)	18 (24.7)	26 (25.7)	
4	19 (9.3)	2 (6.7)	17 (9.8)	10 (13.7)	7 (6.9)	
Unknown	1 (0.5)	0 (0)	1 (0.6)	0 (0)	1 (1.0)	
RNA-HCV level (10^3IU/mL), mean (SD)	5084 (10930.8)	3615 (6119.3)	5338 (11553.6)	4877 (9262.0)	5670 (12996.1)	.430 .494 .656
Fibrosis, N (%)[b]						.293
Level 0	3 (1.9)	1 (4.0)	2 (4.0)	1 (1.8)	1 (1.4)	.182
Level 1	72 (46.2)	12 (48.0)	60 (45.8)	23 (40.4)	37 (5.0)	.431
Level 2	32 (20.5)	2 (8.0)	30 (22.9)	15 (26.3)	15 (20.3)	
Level 3	31 (19.9)	5 (20.0)	26 (19.8)	14 (24.6)	12 (16.2)	
Level 4	8 (5.1)	1 (4.0)	7 (5.3)	2 (3.5)	5 (6.8)	
Level 5	4 (2.6)	2 (8.0)	2 (1.5)	2 (3.5)	(0)	
Cirrhosis, N (%)[b]	6 (3.8)	2 (8.0)	4 (3.1)	0 (0)	4 (5.4)	.209 .081 .142
Familial psychiatric history, N (%)	68 (33.3)	11 (36.7)	57 (32.8)	24 (33.8)	33 (32.7)	.682 .821 1.000
History of mood disorders, N (%)	86 (42.2)	12 (40)	74 (42.5)	47 (64.4)	27 (26.7)	.550 .011 < .001
History of alcohol consumption (g/d), N (%)						.034
0	104 (51.0)	13 (43.3)	92 (52.9)	36 (49.3)	56 (55.4)	.233
< 50	44 (21.6)	5 (16.7)	38 (21.8)	14 (19.2)	24 (23.8)	.415
≥ 50	20 (9.8)	1 (3.3)	19 (10.9)	9 (12.3)	10 (9.9)	
≥ 100	36 (17.7)	11 (36.7)	25 (14.4)	14 (19.2)	11 (10.9)	
Methadone current treatment, N (%)	16 (7.8)	7 (23.3)	9 (5.2)	4 (5.5)	5 (5.0)	.003 .011 1.000
Antidepressant treatment, N (%)	33 (16.2)	10 (33.3)	23 (13.2)	10 (13.7)	13 (12.9)	.013 .030 1.000
HADS anxiety score, mean (SD)	5.41 (3.9)	9.03 (4.7)	4.79 (3.4)	6.03 (3.2)	3.89 (3.4)	< .001 < .001 < .001
HADS depression score, mean (SD)	3.29 (3.4)	6.7 (5.0)	2.71 (2.7)	3.81 (2.9)	1.91 (2.2)	< .001 < .001 < .001

[a]After application of the Bonferroni correction test results with p < .017, these values were considered statistically significant.
[b]156 patients underwent hepatic biopsy (at baseline, 25 depressive and 131 euthymic patients; during treatment, 57 depressive and 74 euthymic patients).
Abbreviations: HADS = Hospital Anxiety and Depression Scale, HIV = human immunodeficiency virus, RNA-HCV = ribonucleic acid of hepatitis C virus.

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Table 2. Descriptive Analysis of the Sample and Comparative Analysis (t scores) Between Groups in TCI-R Dimensions and Subscales[a]

TCI-R Dimensions and Subscales	Baseline (N = 204)			During Treatment (N = 174)		p[b]		
	Total Sample (N = 204)	Depressive (1) (N = 30)	Euthymic (2) (N = 174)	Depressive Induced (3) (N = 73)	Euthymic (4) (N = 101)	1 vs 2	1 vs 3	3 vs 4
Temperament								
Novelty seeking	51.0 (9.2)	51.9 (8.7)	50.8 (9.2)	51.3 (10.1)	50.5 (8.6)	.733	.560	.500
Exploratory excitability	49.5 (9.7)	46.6 (9.6)	50.0 (9.7)	47.9 (10.3)	51.6 (8.9)	.072	.565	.011
Impulsiveness	51.1 (10.5)	55.4 (10.4)	50.4 (10.4)	52.9 (10.7)	48.5 (9.7)	.015	.285	.005
Extravagance	51.8 (10.4)	54.0 (11.4)	51.4 (10.2)	51.5 (10.6)	51.4 (10.0)	.208	.289	.922
Disorderliness	50.3 (10.8)	48.7 (12.7)	50.5 (10.5)	51.5 (11.5)	49.8 (9.6)	.400	.281	.293
Harm avoidance	54.0 (10.5)	58.1 (11.3)	53.3 (10.3)	56.5 (10.7)	51.0 (9.4)	.014	.664	< .001
Anticipatory worry	52.5 (10.2)	55.6 (12.5)	52.0 (9.6)	54.7 (9.8)	50.0 (9.1)	.069	.690	.001
Fear of uncertainty	51.6 (9.8)	51.8 (9.0)	51.6 (10.0)	51.9 (9.8)	51.3 (10.1)	.892	.973	.708
Shyness	51.9 (9.9)	54.1 (10.7)	51.5 (9.8)	52.9 (10.8)	50.5 (8.8)	.189	.603	.119
Fatigability	56.0 (11.8)	62.3 (12.8)	54.9 (11.4)	59.5 (12.0)	51.6 (9.6)	.002	.309	< .001
Reward dependence	48.4 (9.2)	46.5 (9.8)	48.7 (9.1)	47.7 (10.2)	49.5 (8.2)	.303	.644	.306
Sentimentality	48.8 (10.3)	49.9 (10.7)	48.7 (10.3)	48.7 (11.5)	48.7 (9.3)	.560	.635	.980
Openness to warm communications	49.1 (9.1)	47.0 (9.6)	49.5 (9.0)	48.7 (9.9)	50.1 (8.3)	.172	.438	.316
Attachment	49.0 (9.9)	48.0 (10.9)	49.2 (9.7)	49.0 (9.8)	49.3 (9.7)	.560	.677	.799
Dependence	48.1 (10.4)	44.7 (9.0)	48.7 (10.5)	46.4 (10.4)	50.4 (10.4)	.051	.428	.015
Persistence	48.8 (10.4)	46.3 (10.1)	49.2 (10.4)	49.2 (10.6)	49.1 (10.3)	.275	.116	.144
Eagerness of effort	49.8 (11.3)	48.8 (11.9)	50.0 (11.3)	50.9 (11.5)	49.3 (11.1)	.597	.412	.378
Work hardened	47.0 (10.3)	45.1 (9.8)	47.3 (10.4)	47.2 (11.9)	47.4 (9.2)	.271	.386	.914
Ambitious	50.1 (10.2)	47.5 (9.5)	50.5 (10.3)	50.9 (10.0)	50.2 (10.5)	.141	.118	.664
Perfectionist	48.7 (10.1)	46.5 (9.4)	49.0 (10.2)	47.9 (10.2)	49.9 (10.1)	.206	.525	.208
Character								
Self-directedness	47.8 (11.8)	41.0 (15.3)	49.0 (10.7)	45.0 (11.1)	51.9 (9.4)	.001	.748	< .001
Responsibility	47.5 (12.5)	40.6 (14.8)	48.7 (11.7)	45.0 (13.2)	51.4 (9.8)	.001	.142	< .001
Purposefulness	48.2 (12.2)	42.4 (13.1)	49.2 (11.7)	46.7 (12.8)	51.1 (10.6)	.004	.128	.014
Resourcefulness	48.3 (11.2)	44.6 (13.5)	48.9 (10.7)	46.7 (12.0)	50.5 (9.3)	.054	.450	.019
Self-acceptance	49.5 (9.9)	47.1 (11.5)	49.9 (9.6)	48.0 (9.2)	51.2 (9.8)	.165	.672	.034
Enlightened second nature	48.1 (12.4)	42.3 (17.0)	49.1 (11.2)	44.7 (10.5)	50.5 (9.3)	.005	.392	< .001
Cooperativeness	48.2 (10.9)	43.9 (11.6)	48.9 (10.6)	45.2 (10.8)	51.5 (9.8)	.032	.660	< .001
Social acceptance	48.6 (10.2)	47.0 (11.8)	48.8 (10.0)	45.6 (10.0)	51.2 (9.3)	.366	.535	< .001
Empathy	48.7 (10.2)	44.9 (11.5)	49.3 (9.9)	48.0 (10.6)	50.3 (9.3)	.027	.187	.126
Helpfulness	48.3 (9.9)	45.7 (9.7)	48.7 (9.9)	46.2 (9.8)	50.6 (9.5)	.122	.834	.003
Compassion	48.4 (11.0)	45.1 (13.3)	49.0 (10.4)	46.1 (11.4)	51.1 (9.2)	.071	.697	.002
Pure-hearted consciousness	50.0 (10.0)	46.5 (8.9)	50.6 (10.1)	48.4 (10.4)	52.2 (9.5)	.038	.380	.015
Self-transcendence	52.5 (11.4)	51.4 (13.0)	52.7 (11.1)	55.2 (10.6)	50.9 (11.1)	.378	.060	.010
Self-forgetful	51.4 (11.0)	51.7 (11.2)	51.3 (10.9)	52.9 (10.1)	50.2 (11.4)	.851	.607	.106
Transpersonal identification	51.9 (11.0)	49.3 (13.0)	52.3 (10.6)	53.6 (10.7)	51.4 (10.5)	.164	.164	.170
Spiritual acceptance	53.0 (11.4)	52.1 (13.5)	53.2 (11.0)	56.4 (11.7)	50.8 (9.9)	.642	.108	.001

[a]All values are presented as mean (SD).
[b]After application of the Bonferroni correction test results with $p < .017$, these values were considered statistically significant.
Abbreviation: TCI-R = Temperament and Character Inventory-Revised.

final sample included 204 patients, 118 men (57.8%), with a mean (SD) age of 44.39 (10.44) years.

Baseline characteristics of the study population are shown in Table 1. There were some differences between the excluded and included groups. In comparison to the included group, the excluded group had a higher proportion of men (51 [73.9%] vs. 118 [57.8%], $p = .012$), were more likely to have achieved only a primary school education level (40 [58.0%] vs. 95 [46.6%], $p < .001$), were less likely to be employed (39 [56.5%] vs. 143 [70.1%]), had more depressive syndromes (17 [24.6%] vs. 30 [14.7%]), had higher mean (SD) HADS-D (5.09 [4.12] vs. 3.29 [3.44], $p = .001$) and HADS-A (6.88 [4.27] vs. 5.41 [3.93], $p = .012$) scores, and had lower mean (SD) TCI-R personality scores in the self-directedness character dimension (135.94 [36.81] vs. 145.84 [21.83], $p = .016$).

We explored in the final sample past and current psychiatric disorders with a structured interview according to DSM-IV criteria[34] (SCID-I). One hundred thirty-five patients (66.2%) had 1 or more DSM-IV psychiatric disorders: 86 (63.12%) had mood disorders, 56 (42.2%) had anxiety disorders, 85 (62.96%) had substance abuse/dependence disorders, 83 (61.48%) had opioid abuse/dependence disorders, 55 (41.7%) had alcohol abuse/dependence disorders, 59 (28.92%) had cocaine abuse/dependence disorders, 3 (1.5%) had chronic paranoid schizophrenia stabilized, and 3 (1.5%) had eating disorders. Sixty-eight patients (33.7%) had a familial psychiatric history. Thirty patients (14.7%) had a current diagnosis of mood disorder. Table 1 shows the mean (SD) scores for the HADS-D and HADS-A.

Table 2 shows the mean (SD) TCI-R dimension and subscale t scores. For some analyses, we categorized

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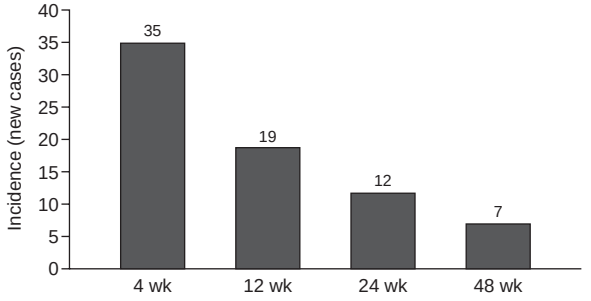
Figure 2. Incidence (new cases) of Depressive Syndrome During Treatment With Pegylated Interferon and Ribavirin



TCI-R dimensions and their respective subscales according to the Spanish validation. The sample was divided into 3 groups (low = < 45, medium = 45–55, and high > 55).

Follow-up. The final cohort was 174 euthymic patients (Table 1) followed during the complete treatment with PegIFN and RBV. One hundred fifty-six patients (89.7%) were treated with PegIFN-α-2a 180 μg weekly subcutaneously and RBV between 600 and 1200 mg weekly depending on their HCV genotype, viral response, and presence of adverse effects. Eighteen patients (10.3%) received PegIFN-α-2b 80 μg weekly subcutaneously and RBV between 600 and 1200 mg weekly, and only 1 patient did not receive RBV due to kidney failure.

There were 73 new cases of depressive syndrome (42%) during the 48 weeks of antiviral treatment. The onset of PegIFN and RBV–induced depression was higher during the first weeks of treatment (Figure 2).

Univariate Analysis

Patients with induced depression (N = 73) as compared with nondepressed patients (N = 101) had a lower education level ($p < .007$), worse employment status ($p < .001$), more history of mood disorders ($p < .001$), and higher HADS-D and HADS-A levels ($p < .001$) (Table 1). The induced-depression group had higher levels of harm avoidance ($p < .001$) and self-transcendence ($p = .010$) and lower levels of self-directedness and cooperativeness ($p < .001$) than the nondepressed group during treatment (Table 2).

There were no differences related to type of PegIFN received ($p = .824$), the dosage of PegIFN-α-2a ($p = .620$), the dosage of PegIFN-α-2b ($p = .772$), and the dosage of RBV ($p = .066$) between both groups with and without induced depression during treatment. A correlation analysis (Spearman's correlation coefficient) between HADS-D mean scores and TCI-R dimension t scores at baseline and at 4, 12, 24, and 48 weeks of treatment was performed (Table 3). Tables 4 and 5 describe the results of the 1-survival function (95% CIs) showing the probability to have depression during 48 weeks of treatment. The same tables show the significance level of the log-rank test between their respective survival curves. Figures 3 and 4 show the survival curves of the most predictive baseline variables in the euthymic HCV patients treated with PegIFN and RBV during 48 weeks.

When patients with baseline depression (N = 30) and euthymic patients (N = 174) at baseline were compared, significant differences in methadone treatment ($p = .003$) or use of antidepressants ($p = .013$) and levels of anxiety (HADS-A) ($p = .001$) and depression (HADS-D) ($p = .001$) were observed (Table 1). The group with depression at baseline had higher levels of harm avoidance ($p = .014$) and lower levels of self-directedness ($p = .001$) (Table 2).

Patients with induced depression during PegIFN and RBV treatment (N = 73) in comparison with those with baseline depression (N = 30) showed significant differences for history of affective disorders ($p = .011$) and current methadone treatment ($p = .011$) and showed lower HADS-D and HADS-A scores ($p < .001$) at baseline (Table 1). Neither TCI-R dimensions nor subscales showed significant differences between these groups of depressive patients (Table 2).

Multivariate Analysis

We used the proportional hazards model of Cox to predict time-dependent variables until induced depression during the PegIFN and RBV treatment in our cohort of HCV patients. We included as covariates all significant variables in the univariate analysis in Table 4 as well as age, sex, immigrant condition, employment status, HCV genotype, HIV coinfection, substance abuse/dependence disorders, and TCI-R categorized scores. The results showed that HADS-D baseline score (HR = 1.113, 95% CI = 1.023 to 1.22, $p = .013$), history of mood disorders (HR = 0.372, 95% CI = 0.220 to 0.629, $p < .001$), and low self-directedness (HR = 0.63, 95% CI = 0.446 to 0.890, $p = .009$) were predictors of induced depression.

We explored a second proportional risks model of Cox with the same potential covariates, but instead of the TCI-R dimensions, we introduced the subscales of these dimensions in the model. We observed that in this case, the predictive variables were history of mood disorders (HR = 0.371, 95% CI = 0.217 to 0.634, $p < .001$) and the TCI-R subscales self-directedness enlightened second nature (HR = 2.939, 95% CI = 1.423 to 6.071, $p = .004$), harm avoidance fatigability (HR = 0.421, 95% CI = 0.237 to 0.749, $p = .01$), and novelty seeking disorderliness (HR = 0.449, 95% CI = 0.248 to 0.815, $p = .008$). In this model, the HADS-D baseline score was not significant.

DISCUSSION

This study examined whether personality traits, as indicated by Cloninger and colleagues' psychobiological

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Table 3. Spearman's Correlations Between Mean HADS-D Scores and TCI-R Dimension t Scores at Baseline and During Treatment

TCI-R Dimension t Scores, Mean	HADS-D Scores, Mean									
	Baseline		4 wk[a]		12 wk[a]		24 wk[a]		48 wk[a]	
	ρ	p	ρ	p	ρ	p	ρ	p	ρ	p
Temperament										
Novelty seeking	0.007	.924	–0.041	.559	–0.061	.390	0.046	.542	0.032	.751
Harm avoidance	0.458	< .001	0.451	< .001	0.450	< .001	0.362	< .001	0.313	.002
Reward dependence	–0.241	.001	–0.241	.001	–0.295	< .001	–0.136	.070	–0.176	.084
Persistence	–0.066	.351	–0.076	.283	–0.022	.758	–0.047	.530	–0.117	.253
Character										
Self-directedness	–0.426	< .001	–0.340	< .001	–0.399	< .001	–0.301	< .001	–0.301	.003
Cooperativeness	–0.372	< .001	–0.328	< .001	–0.407	< .001	–0.303	< .001	–0.157	.123
Self-transcendence	0.116	.097	0.078	.269	0.092	.198	0.032	.669	–0.111	.278

[a]During treatment.
Abbreviations: HADS-D = Hospital Anxiety and Depression Scale-Depression, TCI-R = Temperament and Character Inventory-Revised.

model,[24–26] predicted induced depressive episodes across 48 weeks of treatment with PegIFN and RBV. Our results showed that patients infected with HCV with low self-directedness scores and history of mood disorders and subclinical depressive symptoms at baseline had higher probabilities of induced depression during 48 weeks of treatment with PegIFN and RBV. Moreover, high scores on the harm avoidance fatigability subscale and the novelty seeking disorderliness subscale and low scores on the self-directedness enlightened second nature subscale increased the risk of an induced depressive episode. The incidence of induced depression during the antiviral treatment in our cohort was 42%, which is similar to that reported by others.[8,35]

A review of prospective studies conducted in depressive patients, even after remission of the depressive episodes, shows that patients with a depressive disorder have higher harm avoidance and lower self-directedness scores compared to the general population.[20,21] In agreement with these findings, results of the self-directedness and harm avoidance fatigability subscale were also risk factors for PegIFN-induced and RBV-induced depression in our study.

On the other hand, preliminary prospective studies in HCV patients receiving treatment with IFN showed that personality traits such as neuroticism are risk factors for induced depression.[17,19,36] The fact that harm avoidance is a dimension closely related to neuroticism[37] and to the serotonergic system supports our results.

Furthermore, it has been postulated that IFN causes an alteration in the serotonin network mediated by changes in tryptophan metabolism.[38–42] It seems that major depressive disorder and the neuroticism personality trait have overlapping genetic susceptibilities, especially regarding the serotonergic pathway.[43] For example, polymorphisms in the serotonin transporter gene (5HTTLPR) have been reported to be associated with neuroticism and depression.[44] Moreover, a recent positron emission tomography study shows that subjects with higher thalamic 5-HT binding are more likely to express higher levels of neuroticism and depressive feelings.[45]

Harm avoidance scores have been reported to be predictive of morning hypercortisolemia in depressed subjects. Also, correlations between platelet serotonergic markers (5-HT2a receptors) and harm avoidance in depressed patients have been obtained.[46] It may be argued that people who score high in harm avoidance would be more vulnerable to depression and, on the other hand, that antiviral treatment can induce changes in the serotonergic pathway favoring depression.

Concerning the self-directedness dimension, patients who were immature, with low self-esteem, who blamed other people and external circumstances for what was happening to them had a higher probability of having depressive-induced syndrome during the 48 weeks of PegIFN and RBV treatment (69.3%) than those who scored high on self-directedness (37.2%). Low self-directedness has been associated with personality disorders,[47,48] lifetime psychiatric disorder, and suicide attempts.[49] Some studies suggest that cognitive-behavioral therapy could ameliorate harm avoidance and self-directedness in patients with bulimia nervosa after 1-year follow-up in 12 sessions during 8 weeks.[50] From here on, it might be useful to increase the self-directedness score in those patients who score low to prevent depressive episodes during treatment as Farber et al.[51] have proposed for IFN-induced panic disorder.

With regard to the TCI-R subscales, self-directedness enlightened second nature was the strongest predictor of IFN-induced depression. Patients with low scores on this scale manifest habits of inconsistency, and it is harder for them to accomplish worthwhile goals. In our cohort, the probability of having an induced depression was 70.7% in the subgroup of patients with low scores and 34.4% for those with high scores. An increase in the score of this subscale has been observed in patients with major depressive disorder related to an improvement of depressive symptoms after 1-year follow-up.[52]

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Table 4. Probability of Having Induced Depression at 48 Weeks of Antiviral Treatment: Baseline Variables

Baseline Variables	Probability of Having Depression at 48 Weeks of Treatment	95% CI	p[a]
Age, y			.682
< 36	0.379	0.192 to 0.522	
36–54	0.532	0.397 to 0.637	
≥ 55	0.435	0.241 to 0.580	
Sex			.715
Male	0.452	0.326 to 0.539	
Female	0.575	0.378 to 0.709	
Immigrant			.581
Yes	0.537	0.261 to 0.697	
No	0.474	0.364 to 0.564	
Education level			.002
Primary	0.634	0.473 to 0.747	
Secondary	0.364	0.210 to 0.491	
Higher	0.406	0.144 to 0.588	
Employment status			.595
Employed/housewife	0.480	0.362 to 0.577	
Unemployed/retired	0.522	0.322 to 0.663	
HCV genotype			.366
1	0.483	0.357 to 0.584	
2	0.273	0.004 to 0.469	
3	0.409	0.244 to 0.538	
4	0.708	0.227 to 0.890	
HIV coinfection			.064
Yes	0.425	0.314 to 0.519	
No	0.624	0.423 to 0.755	
Previous interferon treatment			.991
Naive	0.456	0.350 to 0.545	
Retreated	0.548	0.278 to 0.716	
HADS depression score			.001
< 8	0.459	0.356 to 0.546	
≥ 8	0.786	0.416 to 0.921	
HADS anxiety score			.004
< 8	0.447	0.333 to 0.541	
≥ 8	0.612	0.419 to 0.741	
History of psychiatric disorders			.003
Yes	0.605	0.477 to 0.702	
No	0.301	0.126 to 0.441	
History of mood disorders			< .001
Yes	0.743	0.563 to 0.848	
No	0.331	0.200 to 0.441	
History of substance abuse/dependence disorders			.067
Yes	0.607	0.446 to 0.722	
No	0.443	0.299 to 0.557	
Familial psychiatric history			.840
Yes	0.470	0.289 to 0.604	
No	0.481	0.359 to 0.580	
TCI-R dimensions[b]			
Novelty seeking			.753
Low	0.474	0.239 to 0.637	
Medium	0.429	0.300 to 0.534	
High	0.578	0.367 to 0.719	
Harm avoidance			< .001
Low	0.319	0.104 to 0.483	
Medium	0.351	0.203 to 0.471	
High	0.698	0.526 to 0.808	
Reward dependence			.167
Low	0.580	0.380 to 0.716	
Medium	0.395	0.263 to 0.503	
High	0.570	0.304 to 0.735	

(continued)

Table 4 (continued). Probability of Having Induced Depression at 48 Weeks of Antiviral Treatment: Baseline Variables

Baseline Variables	Probability of Having Depression at 48 Weeks of Treatment	95% CI	p[a]
TCI-R dimensions[a]			
Persistence			.429
Low	0.350	0.209 to 0.466	
Medium	0.505	0.348 to 0.625	
High	0.573	0.366 to 0.712	
Self-directedness			< .001
Low	0.693	0.526 to 0.802	
Medium	0.384	0.220 to 0.514	
High	0.372	0.169 to 0.526	
Cooperativeness			.001
Low	0.643	0.475 to 0.757	
Medium	0.421	0.265 to 0.544	
High	0.414	0.191 to 0.576	
Self-transcendence			.007
Low	0.291	0.107 to 0.437	
Medium	0.525	0.322 to 0.668	
High	0.592	0.433 to 0.706	

[a]The significant level of the log-rank test between their respective survival curve.
[b]Low = < 45, medium = 45–55, and high = > 55.
Abbreviations: HADS = Hospital Anxiety and Depression Scale, HCV = hepatitis C virus, HIV = human immunodeficiency virus, TCI-R = Temperament and Character Inventory-Revised.

Other predictive subscales were harm avoidance fatigability and novelty seeking disorderliness. Fatigability is a frequent symptom among patients with decreasing serotonin availability (such as depression), and it relates to the cytochrome P450 2D6 enzyme that modulates the serotonin and dopamine metabolism.[53] Patients who score high on fatigability appear to be asthenic and to have less energy than most people; they need extra rest periods because they get tired very easily. Typically these people recover more slowly than most people from minor illness or stress.

Fatigability is a very prevalent symptom in patients infected by HCV,[54] and it is the symptom that most affects quality of life.[55] Recent neuroimaging data suggest that IFN-α as well as other cytokines of the innate immune response may target ganglia nuclei and contribute to fatigue-related symptoms in medically ill patients.[56] This relationship between depressive symptomatology and fatigability in HCV patients is not related to the hepatic disease, other comorbid diseases, or a previous treatment with IFN.[57] Among the general population, fatigability, impulsiveness, and sentimentalism are the subscales that best predict depression after 4 years' follow-up.[21] In our sample, the probability to have an induced depression in patients who scored high on fatigability was 78.9% vs. 26.0% among those who scored low.

Finally, patients with high novelty seeking disorderliness tend to be quick tempered and disorderly. The novelty seeking dimension has been related to substance and

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Table 5. Probability of Having Induced Depression at 48 Weeks of Antiviral Treatment: TCI-R Subscales[a]

TCI-R Subscales	Probability of Having Depression at 48 Weeks of Treatment	95% CI	p
Novelty seeking			
Exploratory excitability			.140
Low	0.575	0.388 to 0.705	
Normal	0.414	0.266 to 0.531	
High	0.524	0.301 to 0.676	
Impulsiveness			.022
Low	0.344	0.150 to 0.493	
Normal	0.496	0.350 to 0.609	
High	0.626	0.402 to 0.767	
Extravagance			.213
Low	0.543	0.340 to 0.683	
Normal	0.406	0.260 to 0.524	
High	0.547	0.343 to 0.688	
Disorderliness			.053
Low	0.490	0.300 to 0.628	
Normal	0.408	0.238 to 0.540	
High	0.577	0.343 to 0.688	
Harm avoidance			
Anticipatory worry			.001
Low	0.291	0.102 to 0.440	
Normal	0.451	0.288 to 0.576	
High	0.657	0.476 to 0.776	
Fear of uncertainty			.546
Low	0.451	0.239 to 0.604	
Normal	0.468	0.300 to 0.595	
High	0.518	0.327 to 0.688	
Shyness			.124
Low	0.450	0.230 to 0.607	
Normal	0.393	0.268 to 0.496	
High	0.635	0.430 to 0.766	
Fatigability			< .001
Low	0.273	0.091 to 0.418	
Normal	0.351	0.178 to 0.487	
High	0.663	0.505 to 0.771	
Reward dependence			
Sentimentality			.898
Low	0.518	0.293 to 0.672	
Normal	0.432	0.292 to 0.545	
High	0.552	0.342 to 0.694	
Openness to warm communication			.224
Low	0.546	0.362 to 0.677	
Normal	0.361	0.220 to 0.478	
High	0.588	0.366 to 0.732	
Attachment			.649
Low	0.504	0.317 to 0.640	
Normal	0.490	0.326 to 0.614	
High	0.461	0.265 to 0.605	
Dependence			.019
Low	0.574	0.416 to 0.689	
Normal	0.456	0.281 to 0.588	
High	0.408	0.191 to 0.566	
Persistence			
Eagerness to effort			.414
Low	0.421	0.262 to 0.546	
Normal	0.427	0.257 to 0.558	
High	0.590	0.400 to 0.720	
Work hardened			.106
Low	0.546	0.387 to 0.665	
Normal	0.405	0.245 to 0.531	
High	0.494	0.291 to 0.598	
Ambitious			.595
Low	0.370	0.363 to 0.683	
Normal	0.560	0.328 to 0.682	
High	0.466	0.291 to 0.598	

(continued)

Table 5 (continued). Probability of Having Induced Depression at 48 Weeks of Antiviral Treatment: TCI-R Subscales[a]

TCI-R Subscales	Probability of Having Depression at 48 Weeks of Treatment	95% CI	p
Persistence			
Perfectionist			.268
Low	0.551	0.363 to 0.683	
Normal	0.503	0.328 to 0.633	
High	0.396	0.201 to 0.528	
Self-directedness			
Responsibility			.003
Low	0.615	0.440 to 0.736	
Normal	0.460	0.266 to 0.602	
High	0.392	0.213 to 0.515	
Purposefulness			.007
Low	0.640	0.455 to 0.762	
Normal	0.392	0.241 to 0.513	
High	0.448	0.257 to 0.590	
Resourcefulness			.034
Low	0.593	0.414 to 0.717	
Normal	0.431	0.260 to 0.563	
High	0.433	0.246 to 0.574	
Self-acceptance			.187
Low	0.562	0.396 to 0.683	
Normal	0.420	0.271 to 0.538	
High	0.506	0.257 to 0.671	
Enlightened second nature			< .001
Low	0.712	0.550 to 0.816	
Normal	0.390	0.237 to 0.513	
High	0.351	0.146 to 0.507	
Cooperativeness			
Social acceptance			.001
Low	0.658	0.484 to 0.774	
Normal	0.365	0.227 to 0.478	
High	0.446	0.222 to 0.605	
Empathy			.147
Low	0.557	0.364 to 0.692	
Normal	0.409	0.273 to 0.519	
High	0.582	0.316 to 0.745	
Helpfulness			.016
Low	0.600	0.426 to 0.721	
Normal	0.458	0.297 to 0.582	
High	0.392	0.178 to 0.550	
Compassion			.003
Low	0.673	0.474 to 0.801	
Normal	0.421	0.287 to 0.530	
High	0.377	0.199 to 0.516	
Pure-hearted consciousness			.023
Low	0.611	0.404 to 0.746	
Normal	0.483	0.310 to 0.612	
High	0.404	0.402 to 0.695	
Self-transcendence			
Self-forgetful			.225
Low	0.388	0.221 to 0.519	
Normal	0.498	0.285 to 0.647	
High	0.573	0.402 to 0.695	
Transpersonal identification			.152
Low	0.423	0.213 to 0.577	
Normal	0.476	0.296 to 0.610	
High	0.550	0.389 to 0.669	
Spiritual acceptance			.012
Low	0.374	0.142 to 0.544	
Normal	0.440	0.264 to 0.574	
High	0.606	0.453 to 0.717	

[a]Low = < 45, medium = 45–55, and high = > 55.
Abbreviation: TCI-R = Temperament and Character Inventory-Revised.

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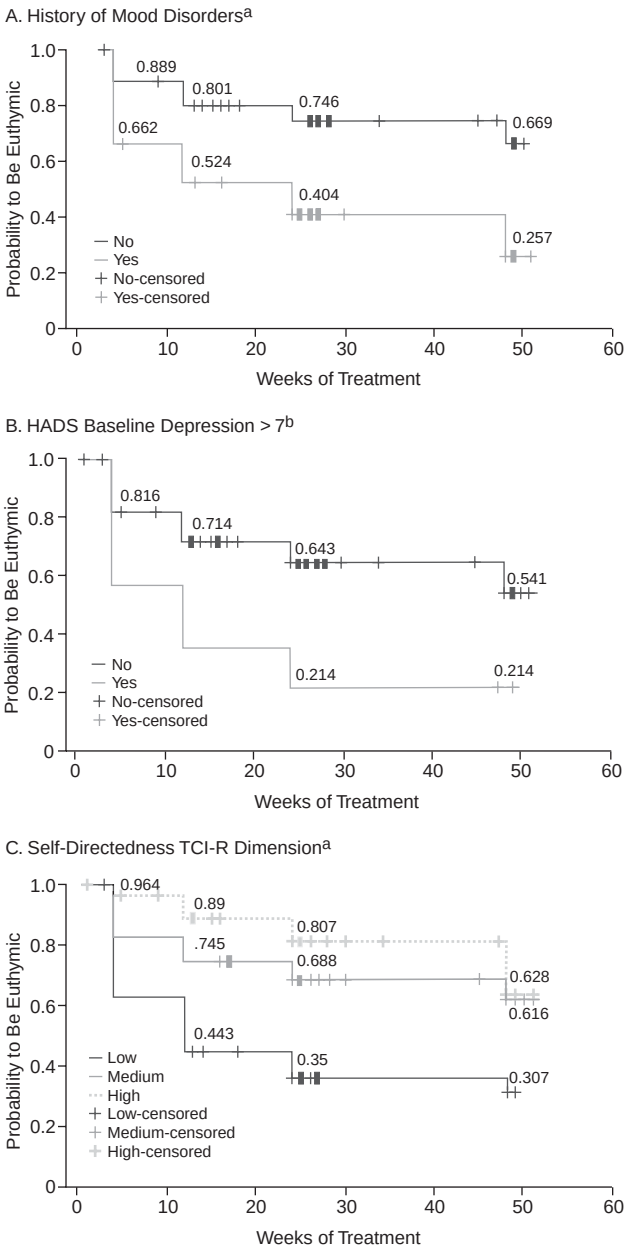
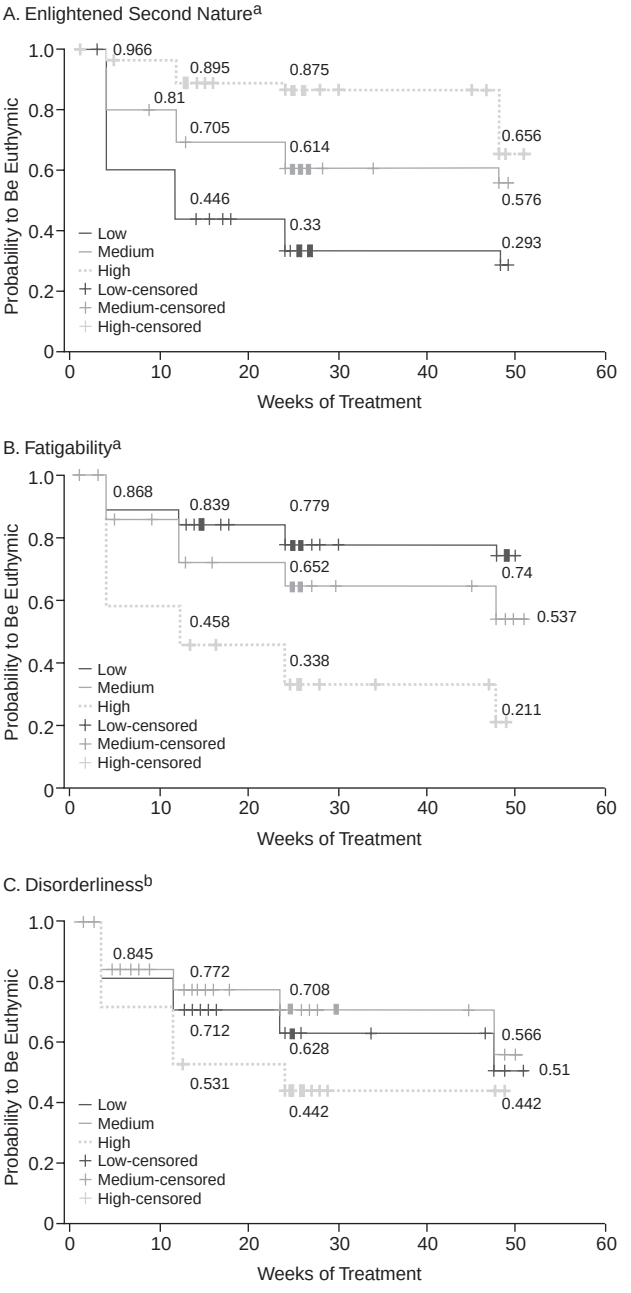
Figure 3. Survival Graphics With Significant Variables



[a]Log rank < .001.
[b]Log rank = .001.
Abbreviations: HADS = Hospital Anxiety and Depression Scale, TCI-R = Temperament Character Inventory-Revised.

Figure 4. Survival Graphics With Significant Variables: TCI-R Subscales



[a]Log rank < .001.
[b]Log rank = .049.
Abbreviation: TCI-R = Temperament Character Inventory-Revised.

alcohol abuse,[58] attention-deficit/hyperactivity disorder,[59] impulse control disorders,[60] and cluster B personality disorders.[61] Moreover, 61.5% of our patients had a lifetime prevalence of substance use disorder.

Personality profiles of patients with induced depression were similar to those of patients with depression at baseline. They had less history of previous affective disorder or current methadone treatment. However, the results of the personality profile of depressed patients at baseline compared to those of the euthymic patients confirmed the association with a high score on the harm avoidance dimension and a low score on the self-directedness dimension.[20,21]

Patients with HCV and depression before starting the PegIFN and RBV treatment had a high level of both anxiety and depression and were under current psychiatric

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treatment. On the other hand, the depressive levels at baseline were a predictive factor, but disappeared in the multivariate analysis. This could be because we eliminated in the analysis patients with depressive syndrome at baseline. Different from other studies of depression induced by interferon,[9–12,14,15] the history of mood disorders was a very relevant predictive variable. This finding could be explained by methodological differences, because some studies did not use a semistructured interview to diagnose past psychiatric disorders in Axis I.

The study has some limitations. Our main limitation is not having a control group; therefore, we cannot exclude that the incidence of depression was due to factors other than the treatment with PegIFN and RBV, for example, having a concomitant personality disorder.[43,44,61] We did not confirm the presence of a personality disorder from a categorical point of view with an Axis II structured interview.

In conclusion, personality traits related to lack of resources and cleverness to cope with a high number of adverse effects and impairment in quality of life during 48 weeks of PegIFN and RBV treatment were important predictors of induced depression. These personality traits together with history of mood disorders and depressive symptoms at baseline define a group of euthymic HCV patients with more probability to suffer from depression during combined treatment with PegIFN and RBV.

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