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No Increase in Depression with Low Dose Maintenance Peginterferon in prior non-responders with Chronic Hepatitis C

Ziad Kronfol, M.D.¹, Heather J. Litman, Ph.D.², Carla Back-Madruga, Ph.D.³, Linas A. Bieliauskas, Ph.D.^{4,5}, Karen L. Lindsay, M.D., M.M.M.⁶, Anna S. Lok, M.D.⁷, and Robert J. Fontana, M.D.⁷ for the HALT-C Trial Group

¹ Depression Center, University of Michigan, Ann Arbor, MI

² New England Research Institutes, Watertown, MA

³ Department of Psychiatry and the Behavioral Sciences, Keck School of Medicine, University of Southern California, Los Angeles, CA

⁴ Neuropsychology Section, Department of Psychiatry, University of Michigan, Ann Arbor, MI

⁵ Psychology Service, Veterans Affairs Health System, Ann Arbor, MI

⁶ Division of Gastrointestinal and Liver Diseases, Keck School of Medicine, University of Southern California, Los Angeles, CA

⁷ Division of Gastroenterology, Department of Internal Medicine, University of Michigan, Ann Arbor, MI

Abstract

Background—Peginterferon and ribavirin treatment of chronic hepatitis C (CHC) is frequently associated with dose-limiting neuropsychiatric toxicity. The purpose of this study is to determine whether prolonged administration of low-dose peginterferon- α 2a is associated with an increase in the rate and severity of depression compared to untreated controls.

Methods—129 non-responders to full dose peginterferon and ribavirin treatment were randomized to low dose maintenance treatment with peginterferon- α 2a 90 ug/wk or no treatment for 3.5 years. Depression was assessed using the Beck Depression inventory (BDI-II) and the Composite International Diagnostic Interview (CIDI) at baseline and at 12, 24, 36, and 48 months. “Clinical depression” was defined as BDI-II ≥ 11 and/or meeting DSM-IV criteria for major depression on the CIDI. Serial cortisol and serotonin plasma concentrations were obtained in a subgroup of patients.

Results—Rates of clinical depression did not significantly differ over time or between treatment groups. Baseline clinical depression was the only significant predictor of clinical depression over time ($p < 0.001$). Rates of clinical depression were also significantly higher in patients experiencing liver disease progression ($p = 0.016$). Antidepressant use did not significantly differ between

Address all correspondence to: Robert J. Fontana, M.D., 1500 E. Medical Center Drive, 3912 Taubman Center, SPC 5362, Ann Arbor, MI 48109-5362, Tel: (734)-936-4780, Fax: (734)-936-7392, rfontana@med.umich.edu.
Dr. Kronfol’s current address is Weill Cornell Medical College in Qatar, Doha, Qatar

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groups. Adjusted whole blood serotonin levels dropped significantly over time ($p=0.04$), but there was no group by time effect.

Limitations—Lack of significant group differences in antidepressant use does not completely preclude significant mood changes masked by antidepressants. Results may differ in treatment-naïve CHC patients or in those receiving full dose peginterferon.

Conclusions—Prolonged low-dose peginterferon- α 2a treatment is not associated with an increase in the frequency or severity of clinical depression in prior non-responder patients with chronic hepatitis C.

Keywords

mood states; neuropsychiatric toxicity; interferon; cytokines; Beck Depression Inventory

Introduction

Treatment of chronic hepatitis C (CHC) patients with interferon and ribavirin therapy is associated with neuropsychiatric toxicity in up to 50% of patients and a frequently cited reason for medication dose reduction or early discontinuation (Raison et al., 2005). Symptoms include depression, anxiety, irritability, fatigue, and other mood and cognitive disturbances (Dieperink et al., 2000; Schaefer et al., 2002). Previous research in this area suggests that mood changes are closely related to the dose and duration of interferon administered (Capuron et al., 1999; Raison et al., 2005; Evon et al., 2009); they are reversible once treatment has been discontinued (Fontana et al., 2008) and can be prevented with a prophylactic anti-depressant such as a selective serotonin reuptake inhibitor (SSRI) (Musselman et al., 2001; Schaefer et al., 2003). Depressive symptoms have been shown to respond well to treatment with an antidepressant, particularly an SSRI (Farah, 2002; Gleason et al., 2002). In spite of recent advances, important unresolved questions include: what is the frequency, spectrum, and risk factors for mood changes associated with prolonged low dose peginterferon treatment of patients with CHC? Are mood changes related to objective changes in liver disease severity? Are the mood changes mediated through alterations in circulating cortisol or serotonin levels?

The Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) Trial is a multi-center, randomized, controlled study designed to determine if prolonged low-dose peginterferon would prevent liver disease progression and reduce the need for a liver transplant. A number of publications have already addressed this important issue and demonstrated a lack of benefit. (Di Bisceglie et al., 2008; Lee et al., 2004; Shiffman et al., 2004). We previously reported on cognitive and mood changes associated with full-dose peginterferon and ribavirin treatment administered in the lead-in phase of the HALT-C Trial (peginterferon α -2a at a dose of 180 ug/ week + ribavirin for up to 48 weeks). Our findings indicate that, interferon-induced depression was noted in 23% and 42% of patients after 24 and 48 weeks combination treatment, respectively (Fontana et al., 2008). The purpose of this study was to assess whether low-dose maintenance treatment with peginterferon α -2a at a dose of 90 ug/ week for 3.5 years was associated with mood changes and to determine the risk factors for such mood changes. In addition, we set out to determine if mood states were related to changes in liver disease severity over time. Based on our prior results and those of others, our hypotheses were that: 1) Prolonged low-dose peginterferon therapy will be accompanied by more depressive symptoms compared to the untreated controls; 2) Depression at baseline (i.e. before treatment) will be a risk factor for clinical depression; and 3) Levels of serotonin but not cortisol will be lower in patients receiving interferon treatment compared to untreated controls (Fontana et al., 2008).

Subjects and Methods

Study design & patient population—The overall study design as well as inclusion and exclusion criteria have been published elsewhere (Di Bisceglie et al., 2008; Fontana et al., 2010; Lee et al., 2004). Briefly, hepatitis C patients with advanced fibrosis or cirrhosis (Ishak fibrosis score ≥ 3 on a scale of 0 to 6) failing to achieve a sustained virological response with peginterferon and ribavirin treatment, and with no history of hepatic decompensation or hepatocellular carcinoma were eligible for enrollment into the randomized phase of the HALT-C Trial. Subjects were randomized to receive peginterferon α -2a at a dose of 90 ug/ week (Pegasys; Roche Laboratories, Nutley, NJ) or no treatment for 3.5 years. Patients were seen every 3 months and underwent a history, physical examination, and laboratory testing to monitor the effects of treatment and assess for clinical endpoints and adverse events. The primary outcome of the study was progression of liver disease within 1,400 days of randomization defined as death, hepatic decompensation (e.g. variceal hemorrhage, ascites, hepatic encephalopathy etc), hepatocellular carcinoma or a Child-Turcotte Pugh score of ≥ 7 (Pugh et al., 1973) on two consecutive study visits. In addition, for subjects with pre-cirrhotic fibrosis at entry, a ≥ 2 point increase in Ishak fibrosis score on a liver biopsy done at month 18 or month 42 following randomization was considered clinically significant histological progression. Only participants in the HALT-C Trial enrolled at the University of Michigan and University of Southern California were asked to participate in this prospective ancillary study of mood status. All details of the study were approved by the local Institutional Review Boards and all patients provided separate written informed consent for their participation in the study.

Psychiatric Assessment

For the assessment of the presence and severity of depressive symptoms, the Beck Depression Inventory (BDI-II), a 21- item self-administered questionnaire was used (Beck et al., 1996). The BDI-II was administered at baseline and at months 12, 24, 36 and 48 of follow-up. A score of < 10 was considered as no depression, 11–14 as minimal depression, 15–19 as mild depression, 20–28 as moderate depression and >28 as severe depression. For a categorical diagnosis of depression, we used the Composite International Diagnostic Interview (CIDI) (Wittchen, 1994), a standardized diagnostic instrument in accordance to the criteria established in the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV). For this study, we used the computerized lifetime version of the CIDI for the depression, anxiety, alcohol and substance abuse modules at baseline and the 12-month version of the depression and anxiety modules at months 12, 24, 36 and 48. “Clinical depression” was defined at each time point as $BDI \geq 11$ or meeting DSM-IV criteria for depression for the previous 12 months on the CIDI. The use of antidepressant medications was recorded, but was not used as a part of the definition of depression. Lifetime alcohol consumption was estimated using a modification of the Skinner survey (Skinner and Sheu, 1982). Years of education referred to the highest level completed. Peginterferon adherence was defined as having received more than 80% of the intended dose up to the three-year time point (Di Bisceglie et al., 2008; Fontana et al., 2010). Liver disease progression was defined as the development of a clinical outcome during the randomized phase or a 2-point increase in Ishak fibrosis score compared to the baseline liver biopsy (Di Bisceglie et al., 2008; Fontana et al., 2010).

Cortisol and Serotonin Assays

In subjects enrolled at the University of Michigan, morning blood samples were drawn and analyzed as previously reported (Fontana et al., 2008). Briefly, plasma cortisol concentrations were measured by immunoassay techniques using an Advia Centaur analyzer (Bayer Diagnostics, Tarrytown, NY). The coefficient of variation for the cortisol assay was

4.3% – 8.0% (Malaguarnera et al., 1998). Whole blood serotonin concentrations were measured using a high-performance liquid chromatography method with fluorescence detection (Bioanalytical Systems, West Lafayette, IN) (Mistler et al., 2006). The dynamic range of the assay was 1–10,000 nM/L, with a coefficient of variation of 3.0%. As platelets are a rich source of serotonin in whole blood and interferon therapy is known to reduce platelet counts, the whole blood serotonin/platelet ratio (adjusted serotonin) was used as a biomarker of whole body serotonin.

Data Analysis

Descriptive statistics of baseline demographic and clinical features are reported as number and percent or mean and standard deviation (SD). Changes in mean values (e.g. BDI-II, cortisol) over time adjusting for baseline scores were assessed using repeated measures analysis of variance (ANOVA). Changes in rates over time adjusting for baseline levels (e.g. antidepressant use, clinical depression) were assessed using generalized linear mixed models. These methods allowed us to use all available data for each patient over time. All analyses were performed at the Data Coordinating Center (New England Research Institutes, Watertown, MA) with SAS statistical software (9.2, SAS Institute, Cary, NC). P-values less than 0.05 were considered statistically significant.

Results

Baseline Features

The baseline characteristics of the 129 patients enrolled in the study did not significantly differ from the 91 non-participants from the two centers (data not shown). The mean age was 51.2 years, 67% were male, 70% were Caucasian and they had an average of 13.6 years of education (Table 1). The majority (67%) were married. The mean lifetime alcohol consumption was 17,347 drinks. Their mean BDI-II score at baseline was 6.4 and 26% had clinical depression. 42% had cirrhosis (Ishak Fibrosis score 5–6) and the mean serum AST was 96 IU/ml. The baseline demographic, clinical and liver disease characteristics did not significantly differ between the patients randomized to peginterferon treatment and the untreated controls (Table 1). During the randomized phase, approximately 30% in each group experienced liver disease progression.

Depression Indices over time

The BDI-II scores for the peginterferon and untreated controls are shown in Table 2. Using an ANOVA model, the only significant predictor of BDI-II scores over time was baseline BDI-II scores ($p < 0.0001$). There were no significant differences between the two treatment groups ($p = 0.81$), over time ($p = 0.99$) or in the interaction of the groups over time ($p = 0.70$). We also examined differences between the peginterferon treated and untreated controls and over time in each of the individual items on the BDI-II scores including the neurovegetative signs of depression (i.e., lack of energy, lack of sleep, and lack of appetite). However, we did not find any significant differences between the groups or over time (data not shown).

Similar results were obtained for major depression based on DSM-IV criteria using the CIDI (data not shown). Although the percent with depression was actually slightly higher in the control group ($p = 0.09$), there were no significant differences over time ($p = 0.65$) or in the interaction between the groups and time ($p = 0.97$).

Because the BDI-II and CIDI provide complementary information regarding different aspects of depression, a new category termed “clinical depression” was defined as a BDI-II ≥ 11 and/or meeting CIDI criteria for major depression. The rates of subjects in both groups with “clinical depression” over time using this definition are shown in Figure 1. Here again,

the only significant predictor “clinical depression” rate over time was baseline “clinical depression” ($p < 0.001$). After controlling for baseline values, there were no significant differences by treatment group ($p = 0.58$), over time ($p = 0.82$), or in the interaction between the groups and time ($p = 0.95$).

Since anti-depressant medications may mask the true rate of depression, we compared the use of antidepressant medications in the treatment and control groups over time (Table 3). At baseline, there were no significant differences in the use of antidepressants between the two groups (31.3% vs 24.2%, $p = 0.38$). After controlling for baseline use, there were also no significant differences in antidepressant use by treatment group ($p = 0.49$), by time ($p = 0.59$), or by the group by time interaction ($p = 0.67$).

Depression and peginterferon adherence

Because the neuropsychiatric toxicity of interferon is dose-dependent (Raison et al., 2005), we also examined the impact of medication adherence (i.e. $< 80\%$ or $> 80\%$ of intended dose) on the frequency and severity of mood changes in the patients randomized to peginterferon (Table 4). Rates of clinical depression over time (after controlling for baseline BDI, $p < 0.001$) did not significantly vary by peginterferon adherence ($p = 0.25$), over time ($p = 0.84$) or by the interaction of both ($p = 0.89$).

Depression and liver disease progression

We also investigated the impact of liver disease progression on mood changes in both groups. During the 3.5 years of follow-up, 36 patients experienced either a two-point increase in Ishak fibrosis score ($n = 18$) or developed a clinical outcome ($n = 18$). The cumulative incidence of liver disease progression was 32% at year 3.5, which is similar to what was reported in the overall HALT-C Trial (Di Bisceglie et al., 2008). The clinical outcomes observed included 1 death, 5 patients with hepatocellular carcinoma, 5 patients with an increase in their Child-Turcotte Pugh scores, 3 patients with variceal hemorrhage, 3 patients with new onset ascites, and 1 patient with spontaneous bacterial peritonitis. When the rates of clinical depression over time in patients with and without disease progression were compared (Table 5) and after controlling for baseline clinical depression ($p < 0.001$), clinical depression was significantly higher among patients with liver disease progression ($p = 0.016$) compared to those with no progression. However, the rates did not change over time ($p = 0.82$), nor was there an interaction between time and liver disease progression ($p = 0.98$).

Biomarkers for Depression—The plasma cortisol values (data not shown) did not vary significantly over time ($p = 0.25$), by treatment group ($p = 0.98$) nor by the group by time interaction ($p = 0.66$). The adjusted serotonin levels were expressed as serotonin/platelet count (Fontana et al., 2008). As indicated in Figure 2, there was a significant drop in adjusted serotonin levels over time ($p = 0.04$). However, there were no significant differences between the groups ($p = 0.40$) or in the group by time interaction ($p = 0.96$).

Discussion

The major hypothesis of the HALT-C Trial was that due to its antiviral and anti-inflammatory properties, prolonged low-dose peginterferon treatment would lead to a significant reduction in the rate of liver disease progression in prior non-responders with advanced fibrosis. The study results, however, indicated no benefit from low-dose maintenance peginterferon in the 1,050 randomized patients followed for 3.5 years in the HALT-C Trial (Di Bisceglie et al., 2008). Those results were confirmed by two similar studies that also used prolonged courses of low dose interferon and failed to show

significant benefit with maintenance therapy in prior non-responders (Afdhal et al., 2008; Fartoux et al., 2007). Since interferon is known to be associated with frequent and potentially severe neuropsychiatric toxicity, (Dieperink et al., 2000; Raison et al., 2005; Schaefer et al., 2002), the current ancillary study was implemented at two of the HALT-C sites to prospectively assess the extent and severity of mood and cognitive changes associated with prolonged low-dose peginterferon treatment. We previously reported our results concerning possible cognitive changes associated with maintenance peginterferon therapy (Fontana et al., 2010). The current results failed to show any evidence of an increase in the frequency or severity of depression that can be attributed solely to the effects of low dose maintenance peginterferon. Scores on the BDI-II as well as rates of CIDI depression did not change during the course of treatment and contrary to our expectations they did not differ significantly between the treated and the untreated groups. Similarly, there were no statistically significant differences in “clinical depression” over time between the treated and untreated groups.

We also examined the possible contributions of different confounding variables, including medication adherence, progression of liver disease and use of antidepressant medications. Medication adherence could be an important issue because only 60% of the peginterferon treated patients in the HALT-C Trial were able to take the prescribed dose of 90 ug/wk for longer than 80% of the time (Di Bisceglie et al., 2008). We therefore postulated that patients with poor compliance (less than or equal to 80% of intended peginterferon dose) would be less depressed than those with good compliance. The results, however, showed that medication adherence was not associated with mood status since the rates of clinical depression did not vary significantly between those who took their peginterferon on a regular basis and those who did not (Table 4).

Severity of liver disease is another issue we examined carefully. Our hypothesis was that patients whose liver condition was deteriorating rapidly would show more evidence of depression than those whose liver disease was stable. Our results did confirm this hypothesis in that patients with liver disease progression during treatment had a higher rate of depression than those whose liver status remained unchanged. Interestingly, these results are at odds with the lack of association between liver disease progression and cognitive function in the same sample (Fontana et al., 2010). However, prior studies have demonstrated a greater frequency of affective disorders in patients with decompensated liver disease compared to those with compensated cirrhosis presumably due to poorer health status and overall prognosis (Cordoba et al., 2003). In addition, results from the overall HALT-C Trial demonstrated a decline in health-related quality of life and sexual health in subjects with disease progression (Snow et al., 2010).

Use of antidepressant medications was allowed during the HALT-C Trial to help maintain patient interest and adherence to the protocol. We therefore hypothesized that since patients taking peginterferon were more likely to be depressed, use of antidepressant medications would be significantly higher in this group of patients. Our results, however, show that the use of antidepressant medications did not significantly differ between the peginterferon treated patients and the control group (Table 3). It is still possible, however, that peginterferon treatment could have been associated with mood changes that have been masked by the use of antidepressant medications. This possibility, however, seems unlikely since use of antidepressant medications was as common in the untreated patients as it was in the treatment group.

The mood effects associated with interferon treatment for CHC are well established (Dieperink et al., 2000; Raison et al., 2005; Schaefer et al., 2002; Evon et al., 2009). However, the majority of studies have been performed with the standard full-dose of

peginterferon (180 ug/wk) in combination with ribavirin and for periods of time generally not exceeding 48 weeks (Fried and Russo, 2003; Hilsabeck et al., 2003; Lee et al., 2006). Results of these studies indicate that the risk of interferon-induced depression is about 20%–40% and that the risk increases with the dose of interferon and its duration (Raison et al., 2005). Similar results have been obtained with high dose interferon monotherapy for malignant melanoma (Musselman, et al., 2001). Furthermore, in many of these studies, depression at the beginning of treatment seems to increase the risk of interferon-induced depression (Cai et al., 2005; Capuron et al., 1999; Dieperink et al., 2003; Hauser et al., 2002). Our study may be the only study in CHC patients to prospectively and in a controlled manner assess the mood effects of low-dose (i.e. 90 ug/ week) maintenance peginterferon using standardized instruments. Our results suggest that the low dose of peginterferon used does not increase the rate of depression even if continued for several years despite substantial reductions in quality of life scores and sexual health assessment in peginterferon treated patients compared to untreated controls (Snow et al., 2010). Only baseline depression and liver disease progression during treatment were associated with an increased risk of depression during low dose maintenance treatment. Although this treatment was not effective in slowing the rate of liver disease progression, our results indicate that prolonged peginterferon therapy can be safely administered without increasing the rate of clinical depression should it prove useful in selected CHC patients or other medical conditions (Di Bisceglie et al., 2008, Eggermont et al, 2008).

With respect to proposed mechanisms of interferon-induced depression (Dieperink et al., 2000; Cai et al., 2005; Capuron et al., 2003, a,b), our results indicate a significant drop in whole blood serotonin levels over time. There are however no significant changes between the groups or in the time by group interaction. Based on our prior results of the lead-in phase in the same patient population (Fontana et al., 2008), we anticipated that normalized serotonin levels would drop significantly over time in the peginterferon group but not in the untreated control group. However, this was not observed. The most likely explanation is that the drop in serotonin levels over time was related to antidepressant treatment, particularly SSRI, thus affecting both interferon-treated patients and untreated controls (Schäfer et al., 2010). It is also possible that this phenomenon is dose dependent and that the dose of peginterferon in the maintenance group of 90 ug per week was not sufficient to affect serotonin levels as did the higher dose of 180 ug per week in the lead-in phase. A final explanation for the lack of a difference in the two treatment groups may relate to the limited number of patients who had blood samples tested. Regarding cortisol levels, our hypothesis was that cortisol levels would remain unchanged over time and between groups since this is what we observed with higher doses of interferon in the lead-in phase (Fontana et al., 2008). Therefore, in the case of cortisol, the null hypothesis was confirmed.

The relationship between cortisol, serotonin and interferon-induced depression remains complex and is still far from being resolved. Both in our previous work (Fontana et al., 2005) and the work of others (Schäfer et al., 2010), no significant relationship between mood changes and the observed changes in serotonin levels could be established. While it has long been known that several pro-inflammatory cytokines, including interferon, stimulate the hypothalamic-pituitary adrenal axis (Cormitt et al., 1996; Sapolsky et al., 1987) and increase neurotransmitter turnover, including serotonin (Dunn et al., 1995; Kronfol and Remick, 2000) the exact mechanisms by which cytokines in general and interferon, in particular, lead to depression has not been completely elucidated. It is possible the increased serotonin turnover is associated with serotonin receptor down regulation (Siever and Davis, 1985). It is also possible that depression is related to neurotoxicity of kynurenine and its metabolites which are stimulated by cytokines (Wichers et al., 2005). Alternatively, inflammatory cytokines, which are increased in major depression (Dowlati et al., 2009; Zorrilla et al., 2001), have been shown to access the brain and interact with

various pathophysiologic pathways known to be involved in depression including neural plasticity (Miller et al., 2009). It is therefore possible that interferon-induced depression could occur without significant changes in either cortisol or serotonin concentrations.

Strengths of this study include the large number of well-characterized CHC patients who were prospectively studied over 3.5 years in a randomized controlled trial. Another strength is the use of standardized psychiatric assessment tools that examined both the scope and severity of depressive symptoms (the BDI-II) as well as the DSM IV diagnosis of depression (the CIDI). A third strength is the examination of key confounding variables such as medication adherence, progression in liver disease and use of antidepressant medications. The absence of mood changes with low dose maintenance peginterferon treatment, although contrary to our proposed hypotheses, seems quite justified by the data. Although HALT-C Trial patients that received peginterferon reported significant declines in quality of life and sexual function over time, we surmise that the low dose of peginterferon used in this study was insufficient to cause substantial mood changes (Snow et al, 2010). It is also possible that our inclusion of only prior non-responders to full-dose peginterferon and ribavirin combination therapy prior to randomization may have selected out highly tolerant patients to the biological effects of interferon. In support of this, a prior prospective study of depression in treatment naïve CHC patients demonstrated that subjects with psychiatric adverse events were significantly more likely to have had early treatment discontinuation compared to subjects without side effects (Evon et al, 2009). Other limitations of our study include the naturalistic approach which allowed the patients access to antidepressant medications, and the use of an untreated control group rather than a placebo-control group. Despite these limitations, we feel that our results add an important dimension to the literature on the mood effects of interferon and provide important information regarding the safety and tolerability of low-dose maintenance peginterferon.

In summary, our results indicate that low-dose maintenance peginterferon treatment was not associated with an increase in the severity or rate of depression in a highly selected group of CHC patients who had not-responded to prior full-dose combination therapy. Only baseline depression and liver disease progression were associated with depression in these patients. Our data suggest that, low dose maintenance peginterferon in non-responder CHC patients has minimal effects on mood in comparison to full dose peginterferon and ribavirin in treatment naïve patients (Evon et al, 2009). Finally, our results suggest that low doses of maintenance peginterferon may be well-tolerated in CHC patients requiring chronic treatment and possibly in patients with other medical conditions such as multiple sclerosis, malignant melanoma, or myeloproliferative disorders that are interferon responsive (Eggermont et al, 2008, Mahon et al, 2002).

Abbreviations

ANOVA	Analysis of variance
BDI-II	Beck-Depression Inventory II
CHC	Chronic hepatitis C
CIDI	Composite International Diagnostic Interview
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders-IV
HALT-C	Hepatitis C Antiviral Long-term Treatment against Cirrhosis Trial
SD	Standard deviation
SSRI	Selective serotonin reuptake inhibitor

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Figure 1. Percentage of patients with “clinical depression” over time. After controlling for baseline clinical depression ($p < 0.001$), there were no significant differences by treatment group ($p = 0.58$), over time ($p = 0.82$), or in the interaction between the groups and time ($p = 0.95$) using repeated measures ANOVA modeling.

Figure 2. Adjusted serotonin levels overtime in peg interferon treated patients and untreated controls

Mean adjusted serotonin levels (nmol/L 10^3 platelets) $\pm$ SE over time in the peginterferon treated and untreated control groups. After controlling for baseline serotonin levels ($p < 0.001$), there was a significant drop in serotonin levels over time ($p = 0.04$), but there were no significant differences in groups ($p = 0.40$) or in the group by time interaction ($p = 0.96$) using ANOVA modeling.

Table 1

Baseline characteristics of the overall study population (n=129) and by treatment group

	Overall N=129 [*]	Peginterferon 90 ug/ week N=66 ^{**}	Untreated controls N=63 ^{***}
Demographics			
Age (years)	51.2 (7.9)	50.2 (7.1)	52.3 (8.6)
% Male	87 (67.4%)	48 (72.7%)	39 (61.9%)
Ethnicity			
% White	90 (70.0%)	44 (66.7%)	46 (73.0%)
% Black	23 (17.8%)	15 (22.7%)	8 (12.7%)
% Hispanic	13 (10.1%)	5 (7.6%)	8 (12.7%)
Educational level (years)	13.6 (2.5)	14.0 (2.5)	13.2 (2.4)
% Married	87 (67.4%)	48 (72.7%)	39 (61.9%)
% Diabetes	27 (20.9%)	16 (24.2%)	11 (17.5%)
Lifetime alcohol consumption (number of drinks)	17347 (25178)	15391 (25475)	19365 (24909)
Baseline Mood status			
Beck score	6.4 (6.6)	6.7 (6.8)	6.0 (6.4)
% Clinical depression [^]	33 (25.6%)	16 (24.2%)	17 (27.0%)
Liver disease parameters			
Ishak Fibrosis score			
2–4	75 (58.1%)	37 (56.1%)	38 (60.3%)
5–6	54 (41.9%)	29 (43.9%)	25 (39.7%)
Serum AST (IU/ml)	96.4 (70.8)	102.2 (79.5)	90.4 (60.5)
Platelets (10 ³ /ml)	162.4 (61.2)	155.5 (57.3)	169.6 (64.6)
Total bilirubin (mg/dl)	0.72 (0.33)	0.70 (0.30)	0.73 (0.35)
Prior antiviral response to pegIFN & ribavirin			
% Breakthrough/relapse	22 (17.1%)	11 (16.7%)	11 (17.5%)
% Lead-in non-responder	107 (82.9%)	55 (83.3%)	52 (82.5%)
% Liver disease progression during randomized phase	36 (29.8%)	18 (28.6%)	18 (31.0%)

Data presented as mean (SD) or n (%).

^{*} The sample size for educational level and alcohol consumption was n=128, baseline BDI-II score was n=125, and for development of liver disease progression was n=121.^{**} The sample size for alcohol consumption was n=65, baseline B-II score was n=64 and for development of liver disease progression was n=63.^{***} The sample size for educational level was n=62, for baseline BDI-II score was n=61 and for development of liver disease progression was n=58.[^] Clinical depression is defined as either a BDI-II ≥ 11 or fulfilling the DSM-IV criteria for major depression during the previous 12 months on the CIDI.

Table 2

BDI-II scores over time by treatment group.

Visit	Peginterferon 90 ug/ week		Untreated controls	
	mean +/- SD	N	mean +/- SD	N
Baseline	7.1 + 7.1	66	6.3 + 6.3	63
12 month	7.7 + 7.4	62	6.5 + 7.5	56
24 month	7.0 + 7.4	59	6.4 + 7.2	55
36 month	7.6 + 7.8	56	6.7 + 8.1	51
48 month	6.0 + 6.9	47	6.1 + 8.4	51

After controlling for baseline BDI-II scores, ($p < 0.001$), there were no significant differences between the treated and control groups ($p = 0.81$), over time ($p = 0.99$), or in the interaction between groups and time ($p = 0.70$) using repeated measures ANOVA modeling.

Table 3

Antidepressant use over time in the peginterferon treated patients and untreated controls.

Visit	Peginterferon 90 ug/ week		Untreated controls	
	On anti-depressant (%)	N	On anti-depressant (%)	N
Baseline	20 (31.3)	64	15 (24.2)	62
12 month	33 (52.4)	63	25 (43.1)	58
24 month	27 (43.6)	62	25 (42.4)	59
36 month	23 (39.7)	58	23 (44.2)	52
48 month	19 (40.4)	47	22 (40.7)	54

After controlling for baseline antidepressant use ($p < 0.001$), there were no significant differences in antidepressant use by treatment group ($p = 0.49$), by time ($p = 0.59$) or by the group by time interaction ($p = 0.67$) using repeated measures ANOVA modeling.

Table 4 Rates of clinical depression over time in relation to peginterferon medication adherence^{*}

Study visit	≤ 80% of intended peginterferon dose		>80 % of intended peginterferon dose	
	N	Number depressed (%)	N	Number depressed (%)
Baseline	36	9 (25.0)	30	7 (23.3)
12 month	35	12 (34.3)	30	8 (26.7)
24 month	32	10 (31.3)	30	6 (20.0)
36 month	28	10 (35.7)	30	9 (30.0)
48 month	22	6 (27.3)	26	7 (26.9)

^{*} Peginterferon adherence is defined as having received at least 80% of the intended dose for at least 3 years. After controlling for baseline clinical depression ($p<0.001$), the percentage depressed did not vary by peginterferon adherence ($p=0.25$), over time ($p=0.84$) or by the interaction of adherence and time ($p=0.89$) using repeated measures ANOVA modeling.

Table 5

Rates of clinical depression over time in relation to liver disease progression*

Study Visit	No Liver Disease progression		Yes Liver Disease progression	
	N	Number depressed (%)	N	Number depressed (%)
Baseline	85	21 (24.7)	36	10 (27.8)
12 month	83	20 (24.1)	36	14 (38.9)
24 month	80	19 (23.8)	33	11 (33.3)
36 month	77	22 (28.6)	30	12 (40.0)
48 month	70	17 (24.3)	26	10 (38.5)

* After controlling for baseline clinical depression rates ($p < 0.001$), the percentage of people with clinical depression was significantly higher among patients with liver disease progression ($p = 0.016$) compared to those without progression in their liver disease using ANOVA modeling. The proportions did not change over time ($p = 0.82$), nor was there an interaction between time and liver disease progression ($p = 0.98$).