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Pegylated Interferon Pharmacokinetics and Self-Reported Depressive Symptoms During Antiviral Treatment for Chronic Hepatitis C

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Abstract

Background—Pegylated interferon-2a (PegIFN-2a) + ribavirin treatment for chronic hepatitis C is often associated with depressive symptoms. Previous studies have failed to explore whether PegIFN-2a pharmacokinetic variability plays an etiologic role in PegIFN-2a-induced mood disorders. The objective of this investigation was to evaluate the association between trough PegIFN-2a concentration at treatment week 4 ("PegIFN-2a $Cmin_4$") and an increase in depressive symptoms.

Methods—Using data from Virahep-C, the association between PegIFN-2a $Cmin_4$ and the following depression outcomes were evaluated using the Center for Epidemiological Studies-Depression scale (CES-D): (1) change in CES-D score from baseline to week 12; (2) greatest difference in CES-D score between baseline and weeks 4, 12, or 24; and (3) occurrence of severe depressive symptoms (CES-D greater than 23) at weeks 4, 12, or 24. One post-hoc analysis examined whether PegIFN-2a exposure during the first week of treatment was associated with change in CES-D score from baseline to week 4.

Results—No significant associations between PegIFN-2a $Cmin_4$ and the depression outcomes were observed ($p>0.05$). Exploratory analyses suggest a possible relationship between PegIFN-2a exposure during the first week of therapy and CES-D score change from baseline to week 4 ($p=0.03$).

Conclusions—PegIFN-2a concentration levels from baseline to week 4 do not predict the onset and severity of depressive symptoms during 24 weeks of antiviral therapy; however PegIFN-2a levels during the first week of treatment may predict depressive symptoms in the first 4 weeks, earlier than anticipated and warrants further exploration.

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Introduction

Pegylated interferon (PegIFN) plus ribavirin (RBV) have provided the backbone to antiviral therapy for chronic hepatitis C viral (HCV) infection and will continue to be included in triple therapy formulations with directing acting antivirals[1–3]. PegIFN-based treatment for HCV is often poorly tolerated by patients due to the side effect profile of PegIFN, which can include flu-like symptoms, hematologic changes, and serious neuropsychiatric symptoms such as depression, insomnia and irritability[4]. Even as pharmacological advances in HCV treatment are rapidly progressing, PegIFN-based regimens remain the standard of care for many patients, including those with less common HCV genotypes and those who live in countries where treatment with newer generation antiviral agents are cost prohibitive[5,6]. Therefore, a better understanding of potential factors associated with the onset and severity of PegIFN side effects is warranted.

Major depression induced by PegIFN, technically referred to as a “substance (interferon)-induced mood disorder” according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR), occurs in approximately one of four HCV patients during antiviral therapy[7]. Depressive symptoms, in general, may occur in up to 60% of treated patients[8,9]. Clinical experience and research demonstrate somatic side effects, such as flu-like symptoms and fatigue, may occur as early as 24 to 48 hours following PegIFN injection[10,11]. In contrast, the onset of neuropsychiatric side effects, such as mood disturbance and depressive symptoms, more commonly occur between weeks 8 and 16 of treatment[9,12,13]. PegIFN-induced mood disorders such as depression appear to be associated with the antiviral treatment dose as well as patient characteristics. Unfortunately, unmanaged depression is a leading cause of dose reductions and premature treatment discontinuations[1,14,15]. As a result, PegIFN-induced depressive symptoms can greatly compromise treatment outcomes.

Two FDA-approved PegIFN formulations are available for the treatment of chronic HCV, PegIFN alpha 2a (PegIFN-2a) and PegIFN alpha 2b (PegIFN-2b). PegIFN-2a is more commonly administered as it is generally accepted to have a more favorable pharmacokinetic profile as compared to PegIFN-2b and fewer side effects[1]. PegIFN-2a is administered subcutaneously once weekly at a fixed dose of 180 μg. The pharmacokinetic profile of PegIFN-2a is characterized by a modest volume of distribution (8 L), extended time to maximum concentration (80 hours), and slow rate of clearance (60–100 mL/hr). Due to similar absorption and elimination half-lives following PegIFN-2a administration, 50 and 65 hours, respectively, interferon concentrations remain similar between dosing intervals, well before reaching steady state concentrations, which are generally obtained within 4 to 6 weeks of treatment[16]. However, substantial inter-patient variability in drug exposure has been demonstrated with PegIFN-2a, with body mass index, race, genetic markers, and other patient factors proposed as possible mechanisms[17–20].

Research to identify risk factors for PegIFN-2a-induced mood disorders has been hampered by variability in study design as well as by a lack of understanding of underlying biologic mechanisms[7,9,21]. To date, the strongest predictor of depressive symptoms occurring during PegIFN-2a treatment is baseline depression, as measured using a standardized

depression instrument[7,21,22]. Other patient characteristics, such as younger age, lower social support, and endorsement of a single depression detection item ("Are you feeling depressed, sad, or blue") at baseline have also been associated with new-onset depression during PegIFN-2a treatment[12]. With regard to biological mechanisms, depletion of serum tryptophan and increase in kynurenine have been explored as possible triggers for PegIFN-2a-induced depressive symptoms[13,23]. Increased levels of proinflammatory cytokines such as sIL-2r, TNF-α, IL-6, and IL-10 at baseline have also been positively associated with PegIFN-2a-associated depressive symptoms[24,25]. Additionally, IL-1Ra, IL-8, IL-10 and TNF-α have been shown to significantly increase as early as one week after initiating PegIFN-2a therapy, whereas other proinflammatory cytokines, such as IL-6, increase much later in therapy, typically after 4 to 6 weeks[26]. Given the support for biological underpinnings of PegIFN-2a-induced depressive symptoms, other biological mechanisms, such as PegIFN-2a pharmacokinetic variability, may play an etiologic role. Previous studies have failed to examine the relationship between PegIFN-2a pharmacokinetic variability and the onset and severity of depressive symptoms during antiviral therapy for chronic HCV.

The primary objective of this study was to determine if trough PegIFN-2a concentration at treatment week 4 (hereafter called "PegIFN-2a $Cmin_4$") was associated with change in depressive symptoms from baseline to week 12, as measured by the Center for Epidemiological Studies-Depression scale (CES-D)[27] in HCV patients receiving PegIFN-2a/RBV therapy. Planned secondary objectives were to evaluate if PegIFN-2a $Cmin_4$ was associated with the greatest change in CES-D score from baseline to treatment week 4, 12, or 24, and to evaluate if PegIFN-2a $Cmin_4$ was associated with the onset of severe depression, defined as a CES-D score greater than 23, at any point during the first 24 weeks of treatment.

Methods

Study Design

This was a longitudinal prospective study that utilized data collected for the NIH-funded Virahep-C study[28]. Prospective data were collected from 401 adults with chronic HCV genotype 1 infection enrolled at eight medical centers in the United States to evaluate factors associated with antiviral treatment response. Inclusion and exclusion criteria have been previously published[28], but important to the purpose of this study, exclusion criteria for the parent Virahep-C study included: a) any current (within past 6 months) severe psychiatric disorder such as depression and b) a prior suicide attempt, hospitalization for psychiatric disease, or a period of disability or impairment due to psychiatric disease within the past five years. Exclusion criteria were determined by the Virahep-C primary investigators. Patients whose psychiatric disorders were controlled by medication and were deemed psychologically stable by the investigator were eligible for participation. During the screening visit and at every clinic visit, investigators relied upon patient self-report of depression via three Depression Detection and Management (DDM) Questions: "Since your last visit, have you felt depressed, sad or blue most of the time?…Have you often felt helpless about the future?"…and Have you had thoughts about harming or killing yourself

or others?" Investigators and personnel were aware of these responses and used them to make clinical decisions about how to manage depression (e.g., dose modifications, prescribe an antidepressant, referral to a psychiatrist, psychotherapy).

Participants were treated with PegIFN-2a 180 μg/week and RBV 1200 or 1000 mg/day, based upon body weight of 75 kg or less, respectively. PegIFN-based regimens are notorious for inducing various states of neuropsychiatric symptoms alone or in combination with other drugs[7,29]. In contrast, a study of monotherapy RBV versus placebo control demonstrated no statistically significant differences in adverse events, including depression[30]. Adherence to taking PegIFN-2a injections and RBV pills in the Virahep-C cohort has been previously established with results of greater than 90% adherence rates[31]. All subjects were treated for a minimum of 24 weeks; those with detectable viremia at week 24 ("nonresponders") were discontinued from therapy per protocol, whereas subjects with undetectable or indeterminate HCV RNA at 24 weeks were continued on therapy for an additional 24 weeks, for a total of 48 weeks. All participants were followed for at least another 24 weeks after treatment discontinuation. All subjects provided written informed consent and the studies were approved by the Institutional Review Boards of the participating sites. This analysis was approved by the Biomedical Institutional Review Board at the University of North Carolina in Chapel Hill.

Subjects

Of the 401 participants from the complete Virahep-C study population, 25 had non-evaluable PegIFN-2a concentration data per Roche Molecular Diagnostics, and thus were ineligible for inclusion in this study. Therefore, data from 376 subjects were included in this study.

Measures

PegIFN-2a concentrations—Specific details of the pharmacokinetic study design for Virahep-C have been previously published[32]. For the purpose of this investigation, serum PegIFN-2a concentrations were obtained prior to the first injection of PegIFN-2a (i.e., baseline) and on treatment days 1, 2, and 3. Additionally, trough PegIFN-2a concentrations were drawn at the end of weeks 1, 2, 4, 8, 12, 24 and 48 prior to patients receiving their next scheduled PegIFN-2a injection. PegIFN-2a concentrations were measured by enzyme-linked immunoassay (Roche Molecular Diagnostics; Alameda, CA). The assay had a lower limit of sensitivity of 250 pg/ml and a dynamic range of 350 to 3000 pg/ml. PegIFN-2a concentrations were subject to re-assay if baseline (day 0) samples had measurable concentrations of greater than 350 pg/mL. For PegIFN-2a concentrations noted as 349 pg/mL, the concentration at that time point was presumed to 0 pg/mL due to the lower limit of assay sensitivity. Previous pharmacokinetic studies have demonstrated that PegIFN-2a levels reach steady-state concentrations by eight weeks of once weekly administration of PegIFN-2a [32]. For the purpose of this evaluation, we hypothesized pharmacokinetic variability in trough PegIFN-2a concentration early in the course of therapy (week 4) would predict subsequent change in depressive symptoms later in the course of therapy at week 12.

Depressive Symptoms—The assessment of depressive symptoms for research purposes was evaluated using the CES-D scale[27]. The CES-D is a 20-item self-report questionnaire and scores range from 0 to 63, with higher scores indicative of more severe symptomatology. The CES-D has been used in multiple HCV treatment studies and demonstrates satisfactory reliability and validity[33]. The CES-D was obtained for research purposes only, at baseline and treatment weeks 4, 12, and 24. Assessments were conducted using touch-screen technology and the results were masked from study personnel; thus, the results of the CES-D were not used to make any clinical decisions, such as prescribing an antidepressant. The primary outcome of interest was the difference in CES-D score between baseline and treatment week 12, the time at which previous studies demonstrate that depressive symptoms appear during HCV treatment[12].

Statistical analysis

Descriptive statistics (means, standard deviations (SD), frequencies) were calculated for patient demographics and baseline covariates (n=376). These included: age, sex, race, body mass index (BMI), social support, antidepressant use at baseline, social support, and endorsement of a single depression detection question “feeling sad, blue, or depressed at baseline.”

While the primary outcome measure was the difference between CES-D score at baseline and week 12 based on our previous work[12], two secondary analyses were planned to determine if PegIFN-2a $Cmin_4$ was associated with (1) greatest difference in CES-D score identified between baseline and treatment week 4, 12, or 24 (continuous variable), or (2) severe depressive symptoms at week 4, 12, or 24, defined as a score >23 on the CES-D scale (dichotomous variable).

In the primary and secondary analyses, we conducted unadjusted bivariate analyses between PegIFN-2a $Cmin_4$ and the depression outcome, and followed up with multivariate analyses adjusting for several covariates. In planned multivariate analyses we chose *a priori* covariates that were the most robust predictors of depression in our previous work to determine if PegIFN-2a $Cmin_4$ made an additional contribution (11). A progressive modeling approach was utilized to determine whether these variables influenced the relationship between CES-D score outcome and PegIFN-2a $Cmin_4$. Model 1 included only PegIFN-2a $Cmin_4$ regressed on the outcome and Model 2 included PegIFN-2a $Cmin_4$ regressed on the outcome adjusted for *a priori* covariates. Generalized linear models were used to fit the continuous outcome variables (change in CES-D score from baseline to week 12 or largest change in CES-D score from baseline to week 4, 12, or 24). Box-Cox transformation was utilized to assess whether a transformation of the outcome variable would result in a better fit of the model. Logistic regression was used to model severe depressive symptoms, a dichotomous outcome. The level of significance was set at 0.05 for the primary and secondary outcomes of interest.

Sensitivity analyses were conducted where all participants who were on antidepressants and/or had severe depression (defined as CES-D score > 23) at baseline were excluded from the analysis subset. The adjusted model was re-evaluated for the primary and secondary outcomes of this reduced data set.

One post-hoc exploratory analysis was conducted using the subset of participants who had PegIFN-2a concentrations measured at baseline (prior to the first dose) and over the course of the first week of the study at days 1, 2, 3, and 7. (N=140). Day 7 serum samples were collected prior to administration of the second dose of PegIFN-2a. PegIFN-2a AUC_{1wk} was calculated using these data and regressed on the difference in CES-D score between baseline and week 4 using a generalized linear model[34]. Due to the exploratory nature of these analyses, statistical significance was set at 0.01. All analyses were conducted using SAS version 9.2 (SAS, Cary NC).

Results

Sample Characteristics

The characteristics of the overall Virahep-C study population are described elsewhere[28]. The descriptive statistics for characteristics of the subjects included in the present study are displayed in Table 1.

Longitudinal Changes in PegIFN-2a Concentrations

Figure 1 displays median PegIFN-2a trough concentrations and interquartile ranges at each time point between baseline and treatment week 24. As illustrated in the figure, trough PegIFN-2a concentrations were undetectable at baseline and gradually increased over the first eight weeks of treatment. At or prior to week 8, steady-state concentrations were achieved, a time at which the drug elimination rate is approximately equal to the drug administration rate. Three hundred and forty-six subjects had data available for the predictor variable of interest, PegIFN-2a $Cmin_{4,}$ at this time point and were included in the analyses. The median PegIFN-2a $Cmin_4$ was 14362 pg/mL (range 0 – 49317 pg/mL).

Longitudinal Changes in Depression Scores

Figure 2 shows the distribution of CES-D scores over the first 24 weeks of treatment. There was a statistically significant increase in median CES-D scores from baseline to treatment week 4 ($p<0.01$). There was a slight increase in median CES-D scores from treatment week 4 to week 12 and week 12 to week 24, but the distribution of the scores was similar at weeks 12 and 24 as compared to week 4.

Associations Between PegIFN-2a Concentrations and Depression

Table 2 presents the difference in CES-D score between baseline and week 12 using the unadjusted and adjusted models. PegIFN-2a $Cmin_4$ did not significantly predict change in CES-D score from baseline to week 12 in the unadjusted model ($p = 0.39$) or adjusted model ($p = 0.45$).

In both secondary analyses, similar results were found. When PegIFN-2a $Cmin_4$ was regressed on the greatest difference in CES-D score from baseline to week 4, 12, or 24, PegIFN-2a $Cmin_4$ was not significantly associated with the outcome in unadjusted models ($\beta = 0.46$; Standard Error (SE) = 0.64; $p = 0.48$) or adjusted models ($\beta = 0.55$; Standard Error (SE) = 0.68; $p = 0.42$). Likewise, no statistically significant relationship was found between PegIFN-2a $Cmin_4$ and severe depression as indicated by a CES-D score greater than 23 in

the unadjusted model (OR = 1.02; 95% Confidence Interval (CI): 0.77, 1.34; p = 0.89) or the adjusted model, including baseline CES-D score (OR = 0.95; 95% CI: 0.68, 1.33; p = 0.78).

Sensitivity Analyses

To determine whether baseline antidepressant use or severe depression could have impacted the relationship between PegIFN-2a $Cmin_4$ and new onset depression during HCV treatment, a sensitivity analysis was conducted. A total of 81 participants were excluded: 28 who were taking antidepressants at baseline; 37 who had severe depressive symptoms (CES-D score >23) at baseline; and 16 who had both. Multivariate analyses were re-examined. The findings were similar; PegIFN-2a $Cmin_4$ was not significantly associated with any of the depression outcomes of interest.

Post-hoc Analyses

When the use of trough PegIFN-2a concentrations as a surrogate measure of drug exposure failed to predict the pre-specified primary and secondary outcome measures, we became interested in a more comprehensive view of PegIFN-2a drug exposure that might help explain the onset or severity of depressive symptoms. We had data available from 140 subjects who had concentration data collected at baseline (prior to PegIFN-2a administration) and treatment days 1, 2, 3, and 7. Figure 3 presents the distribution of PegIFN-2a concentrations for these subjects during the first week of treatment. Following the first injection, PegIFN-2a concentrations increased before reaching peak concentrations (C_{max}), approximately three days following drug administration. Although only partially eliminated, PegIFN-2a concentrations decreased by day 7 prior to the second injection. These pharmacokinetic data obtained during the first seven days of treatment were used to calculate a new exploratory predictor variable, PegIFN-2a AUC_{1wk}, the area under the concentration-time curve for the first seven days following the first PegIFN-2a injection. The median PegIFN-2a AUC_{1wk} was 7834 pg/mL (range 804 – 19832 pg/mL).

Unadjusted and adjusted models of PegIFN-2a AUC_{1wk} on CES-D score at week 4 are presented in Table 3. An association between PegIFN-2a AUC_{1wk} and change in CES-D from baseline to week 4 was found although did not reach statistical significance set at a conservative level of $p<0.01$ in either the unadjusted (p = 0.07) or adjusted model (p = 0.03).

Discussion

A better understanding of biopsychosocial mechanisms of depressive symptoms during PegIFN-2a/RBV therapy is needed to identify patients early in treatment who may be at risk for adverse, and sometimes treatment-limiting, side effects. In the present study, data were utilized from a large prospective database to determine if variability in trough PegIFN-2a concentrations early in antiviral treatment may contribute to the onset and severity of depressive symptoms later in treatment. The overwhelming results suggest that change in PegIFN-2a concentration from baseline to week 4 does not play an etiological role in the development or severity of depression during the first 24 weeks of HCV treatment. This was the case regardless of the timing or severity of depression symptoms being investigated.

During a post-hoc analysis, we found a trend for patients with higher drug exposure (AUC) during the first 7 days of treatment to have greater risk of depressive symptoms at 4 weeks into treatment, much earlier than is typically observed clinically. This trend was supported after adjusting for several robust *a priori* covariates known to be associated with new onset depression[12]. This analysis was exploratory so caution is required during interpretation; however, it is possible that variability in PegIFN-2a pharmacokinetics during the first 7 days of treatment exerts an effect on the development of depressive symptoms quite early in treatment[32]. This trend requires further exploration in an adequately powered study.

A few limitations of this study are noteworthy. Self-report instruments, such as the CES-D, are not objective diagnostic tools and cannot be used to make bona fide psychiatric diagnosis. Compared to clinical diagnostic interviews, self-report surveys may tend to over-report depressive symptoms, especially in patient populations such as in HCV, where multiple somatic complaints may mimic depressive symptoms[9]. Secondly, although we were able to evaluate the impact of baseline antidepressant use on depression outcomes (a null finding), the dataset did not permit us to explore the effects of initiating a new antidepressant therapy on depression outcomes. However, from the minimal data available from this dataset, only two patients initiated antidepressant therapy during the first 8 weeks of treatment (more did so after week 24, which was outside the time frame of the current study), therefore these initiations did not likely affect the results of the current study.

Trough concentrations of PegIFN-2a were used as a surrogate measure of actual drug exposure and we were only able to obtain trough drug concentrations after the first week of PegIFN-2a administration. Therefore, the classical area under the curve could not be calculated. Because the metabolism of PegIFN-2a is not well characterized and the rate of elimination is highly variable (84-353 hours)[35], polymorphisms in mechanistic pathways for metabolism and elimination could result in variability in overall drug exposure, which could not be understood using the data collected for this investigation. Previous investigations have shown that variability in pharmacodynamic response, as measured by sustained virologic response following administration of PegIFN-2a-2b and interferon-2b, were not predicted by pharmacokinetic differences in the two formulations[36]. However, these formulations were not the same as those used in the current investigation. Other pharmacodynamic outcome variables, such as 2,5-OAS concentrations and early virologic response, have been predicted by variability in PegIFN-2a pharmacokinetics[32]. Future investigations to assess AUC beyond the first week of therapy may be able to demonstrate a link between PegIFN-2a and onset of depressive symptoms; however, the limited exposure data available in this current investigation failed to support that association. The mechanism for variability in virologic response continues to be poorly understood. Provided a link between sustained virologic response and onset of PegIFN-2a-induced adverse events, future investigations may utilize other markers such as early virologic response (EVR) or changes in 2,5-OAS levels as predictors of treatment induced adverse events that occur later in the course of therapy, such as depression.

Compared to the null findings reported in this study, a number of other putative biological mechanisms have been associated with the development of depression during HCV antiviral therapy. Pretreatment levels of proinflammatory cytokines[24,25], increases in kynurenine,

and decreases in tryptophan and the serotonin metabolite 5-IAA during treatment[13,23,37,38], as well as genetic factors[39,40] have all been linked to PegIFN-2a-associated depression. These biological pathways may be more fruitful avenues for future research investigation.

In sum, trough PegIFN-2a levels at week 4 of HCV treatment does not impact the onset or severity of depressive symptoms in the first 24 weeks of treatment, when the majority of depressed cases occur[12]. However, based on preliminary findings from our post-hoc analyses, variability in PegIFN-2a concentrations during the first week of treatment may be associated with early signs of depressive symptoms. Thus, the time frame in which PegIFN-2a pharmacokinetics exert an impact on pegIFN-2a-induced mood disorders may occur much earlier than anticipated. Beyond these preliminary findings, our thorough examination of these factors, along with the methodological strengths of this study such as a large sample size and longitudinal design, provide strong evidence that variability in PegIFN-2a exposure at week 4 is not a significant predictor of depressive symptoms during PegIFN-2a-based treatment for HCV.

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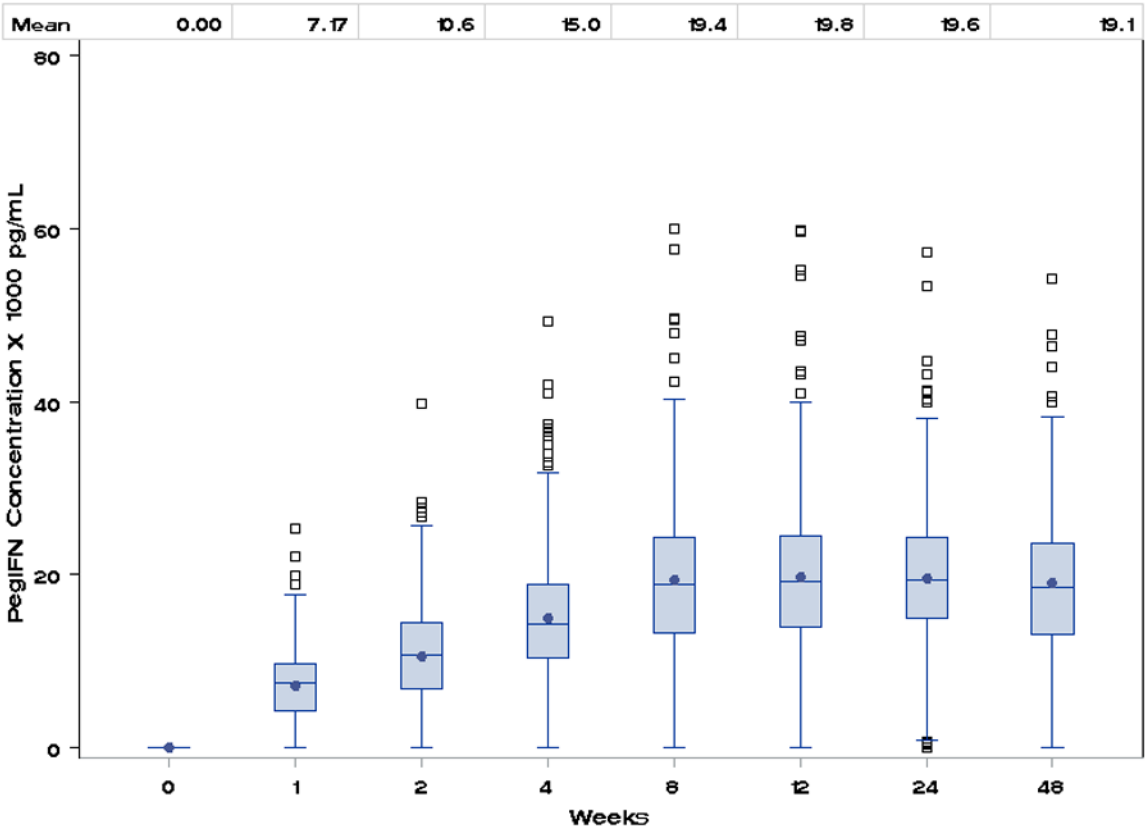

Figure 1.

Box plot distribution of trough PegIFN-2a concentration value (1000 pg/mL) from baseline to week 24.

Note: [a] Solid circles represent the mean serum trough PegIFN-2a concentration values (1000 pg/mL).

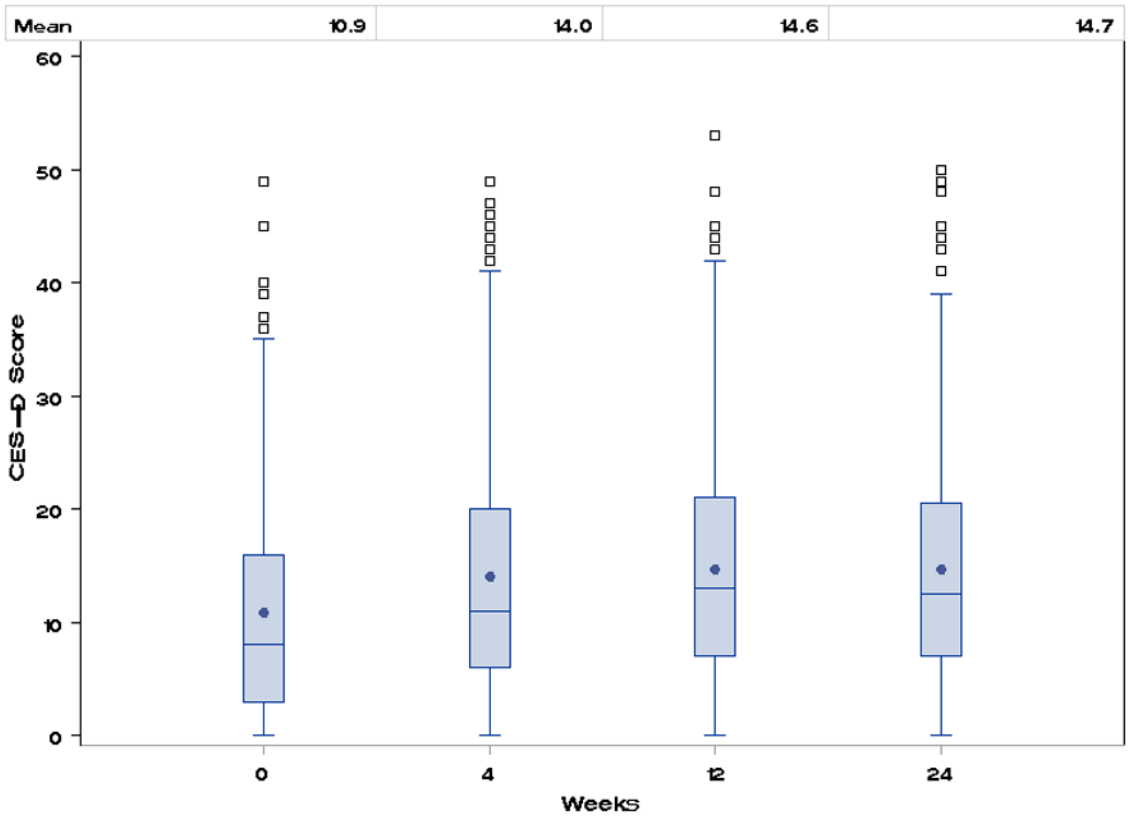

Figure 2.

Box plots of CES-D scores from baseline to week 24.

Note: ***p<0.01 for comparison to baseline (two-sample t-test)

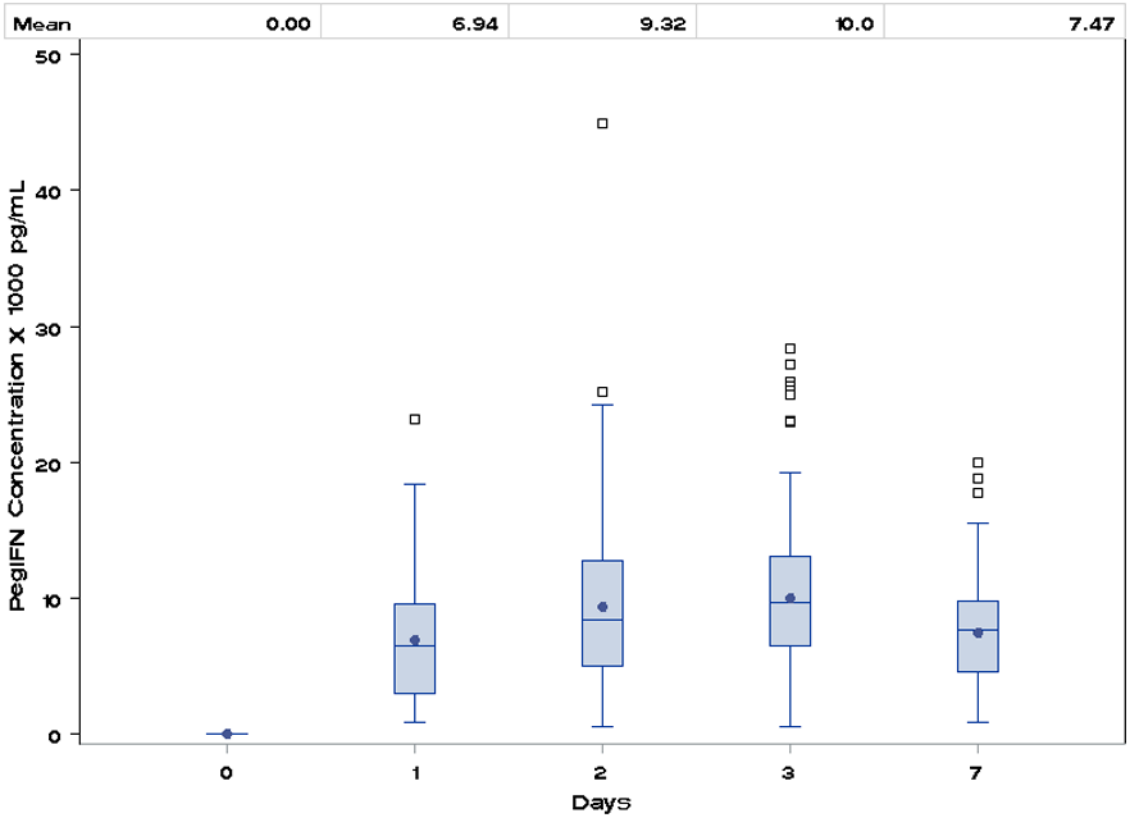

Figure 3.
Box plot distribution of PegIFN-2a concentration value (1000 pg/mL) from baseline to day 7.

Table 1

Patient Baseline Characteristics (n=376)

Baseline Characteristic	
Age[a] mean (SD)	47.9 (7.9)
Gender, n (%)	
Male	246 (65%)
Female	130 (35%)
Race, n (%)	
African American	187 (50%)
Caucasian	189 (50%)
Body Mass Index[b], mean (SD)	29.4 (6.0) kg/m^2
Baseline Antidepressants, n (%)	
Yes	44 (12%)
No	332 (88%)
Felt “Sad, Blue, Depressed” [a], n (%)	
Yes	20 (5%)
No	355 (95%)
Social Support[c], mean (SD)	79.6 (19)
CES-D[d], mean (SD)	10.9 (9.4)

Note: SD=standard deviation; CES-D=Center for Epidemiological Studies-Depression Scale;

[a] n=375;

[b] n=372;

[c] n=370;

[d] n=371

Table 2

Results of unadjusted and adjusted models of PegIFN-2a Cmin predicting difference in CES-D score from baseline to week 12

	Model 1		Model 2	
	N=325		N=314	
Variable	**β (SE)**	**p-value**	**β (SE)**	**p-value**
PegIFN $Cmin_4$ *	0.59 (0.68)	0.39	0.49 (0.65)	0.45
Age			−0.02 (0.07)	0.79
Body Mass Index			−0.10 (0.09)	0.26
Gender (Female)			−1.46 (1.12)	0.19
Baseline Antidepressants			−0.38 (1.68)	0.82
Social Support			0.06 (0.03)	0.03
Feeling “Sad/Depressed/Blue”			−4.48 (2.46)	0.07

Note: SE= Standard Error

* Unit change = 10000 pg/mL

Model 1: Difference between Week 12 and Baseline CES-D score = PegIFN-2a $Cmin_4$

Model 2: Difference between Week 12 and Baseline CES-D score = PegIFN-2a $Cmin_4$ + Age +BMI + Gender + Anti-Depressant Use + Feeling Sad/Depressed/Blue

Table 3

Exploratory analyses using PegIFN-2a AUC_{1Wk} to predict CES-D difference score from baseline to week 4

	Model 1[a] N=129		Model 2[b] N=128	
Variable	**β (SE)**	**p-value**	**β (SE)**	**p-value**
PegIFN AUC_{1wk} [c]	0.38 (0.21)	0.07	0.47 (0.22)	0.03
Age			−0.05 (0.10)	0.61
BMI			0.14 (0.14)	0.31
Gender (Female)			3.29 (1.97)	0.10
Baseline Antidepressants			−4.26 (3.04)	0.16
Social Support			0.02 (0.05)	0.58
Feeling “Sad/Depressed/Blue”			−1.44 (4.18)	0.73

Note: SE= Standard Error

[a] Model 1: Outcome = PegIFN-2a AUC_{1Wk}

[b] Model 2: Outcome = PegIFN-2a AUC_{1Wk} + Age + BMI + Gender + Anti-Depressant Use + Feeling Sad/Depressed/Blue

[c] Unit change = 1000 pg/mL