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HEALTH-RELATED QUALITY OF LIFE IN SUBJECTS WITH HCV/ HIV COINFECTION: RESULTS FROM ACTG 5178 Study

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Abstract

Though health-related quality of life (HRQOL) is diminished in HCV/HIV, the relationship between virologic response or maintenance therapy with HRQOL in this population is unknown. ACTG 5178 was a phase 2, randomized trial, with 3 steps: Step 1: all subjects received PEG-IFN/ribavirin (P/R) for 12 weeks. Step 2: subjects who failed to achieve early viral response (EVR) were randomized to PEG-IFN or observational control for an additional 72 weeks. Step 3: subjects with EVR from Step 1 continued on P/R for a total of 72 weeks with 24 weeks follow-up off therapy. HRQOL, symptom distress and depression levels were measured at multiple time points. In Step 1 (n=329), there was a significant decline in HRQOL in all dimensions. In Step 3 (n=169), the overall HRQOL and 3 of its 8 dimensions (general health, role function and pain score) were increased, and achievement of SVR was associated with increased general health and cognitive function. In the Step 2 group (n=85), there was no significant change in HRQOL and no significant difference between groups (PEG-IFN vs. observational control). There was a significant decline in HRQOL during the initial 12 weeks of therapy. Thereafter the HRQOL profile differed for subjects with EVR vs. without EVR. Maintenance therapy with PEG-IFN had no impact on the HRQOL.

Keywords

HCV; HIV; coinfection; treatment; health related quality of life

INTRODUCTION

The prevalence of hepatitis C virus (HCV) co-infection in the US among those with human immunodeficiency virus (HIV) infection is approximately 15 – 30%[1]. The gold-standard primary end point for HCV treatment trials is sustained virologic response (SVR) defined as the proportion of subjects with no detectable viral replication 24 weeks after a full course of treatment. Currently the SVR rate with pegylated interferon and ribavirin (P/R) is lower in HCV/HIV co-infected individuals compared to those with HCV mono-infection. Though SVR is an accurate measure of clearance of viral replication, it does not evaluate the benefit

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as perceived by the patient. Patient reported outcomes (PRO) have the unique advantage of measuring the effects of treatment on the physical, mental and social well-being of the individual. PRO may provide useful insights into the effects of P/R on the quality of life (QOL) of individuals with HCV/HIV co-infection. ACTG 5178 was a prospective, Phase 2 clinical trial designed to evaluate the role of pegylated interferon alfa (PEG-IFN) maintenance therapy in HCV/HIV co-infected patients[2]. The aim of this secondary analysis was to evaluate the health-related quality of life (HRQOL) profile of this population, as well as its relationship with subjects' distress and depression levels.

METHODS

Subjects and study design

The ACTG 5178 was a phase 2, prospective, open-label, two-arm, long-term maintenance therapy study to determine whether long-term maintenance of PEG-IFN reduced the rate of liver fibrosis progression in subjects with HCV/HIV co-infection who had failed to achieve early viral response (EVR). Both HCV treatment-naïve and previously treated subjects were enrolled.

The study had three steps: In step 1, Chronic HCV/HIV co-infected subjects, consistent with liver biopsy results within 2 years, who were either HCV treatment naïve or failed to achieve HCV sustained viral response (SVR) for at least 12 weeks to any interferon-based therapy received P/R treatment for a minimum of 12 weeks. In step 2, subjects who failed to achieve EVR from step 1 or from P/R received separately from ACTG 5178 went through a second liver biopsy to confirm their chronic viral hepatitis and fibrosis stage and were randomized within 6 weeks of biopsy to either the treatment group to continue PEG-IFN treatment for another 72 weeks or to the observational control group. In step 3, subjects from step 1 who achieved EVR continued on P/R treatment for a total of 72 weeks and were then followed off treatment for an additional 24 weeks. More detailed description of the study design and the primary analysis on the effect of long term PEG-IFN treatment in non-EVRs between the treatment and control groups can be found in a previous publication[2].

In ACTG 5178, patient-reported health related QOL (HRQOL), distress and depression symptoms were collected at step 1 entry and 12weeks; entry to step 2 and step 2 +12weeks, +24weeks, +48weeks, and +72 weeks; and entry to step 3 and step 3 +12weeks, +24weeks, +48weeks, +54–60weeks, and +78–84weeks.

Health Related Quality of Life Measurement

ACTG QOL surveys were used as PRO to assess 8 different dimensions of subjects' health status[3,4]. These surveys included 21 questions which can be combined and recoded to 8 variables of scale 0–100 to assess subjects' general health perceptions, physical function, role function, pain, social function, mental health, energy/fatigue and cognitive function with higher scores reflecting better health status. Summation of these 8 dimensions was used to reflect subjects' overall health status.

Distress Level Measurement

Subjects' distress levels were measured by a symptom distress module[5]. The twenty questions included in this module evaluated subjects' distress levels based on presence of different distress symptoms, e.g., fatigue, fever, pain, loss of memory, etc., and the level each symptom affects the subjects' life with a range of 1–4, where higher value in all these questions reflecting a more severe distress level. The summation of these 20 questions was calculated to represent the overall distress level.

Depression Level Measurement

Subjects' depression levels were measured by a short form of the Center for Epidemiologic Studies Depression Scale (CES-D) with 10 questions. Each question was recoded into a variable of range 0–3 with a higher value reflecting a less depressive, better health status. The summation of these 10 questions was calculated to represent the overall depressive level. With the recoding, a cutoff ≤ 20 represents depressive symptoms [6,7].

Potential confounders

We considered the following covariates: gender, race, prior treatment of HCV and presence of cirrhosis. All have been associated with variation in reported quality of life measures in prior studies.

Subjects entering step 2 had liver biopsies at the step entry. These biopsy results better reflected subjects' liver disease status compared to the presence of cirrhosis at study entry and were used when examining whether cirrhosis affected HRQOL both at step 2 entry and over time for subjects without EVR.

Statistical analysis

Because entry to step 2 vs. step 3 was conditional on the outcome of step 1, HRQOLs were analyzed separately by study step. HRQOL at entry to each step was compared according to prior HCV treatment, gender, race and liver disease severity using analyses of covariance and linear regressions.

Changes of HRQOL over time within steps were evaluated using linear mixed effects models with time as a continuous covariate and controlling for variables that were significant at each step's entry. Random intercepts and slopes were included to account for correlations between repeated measurements within subjects. Unstructured variance-covariance structure was specified between random intercepts and random slopes. The changes in outcome variables over time were based on the estimated mean slopes from the linear mixed effects models.

In the linear mixed effects models for subjects on step 2, the mean of the random intercepts and random slopes were allowed to be different for PEG-IFN treatment group and the observational control group. The estimated means of slopes were compared between treatment groups to test for the treatment effect. When modeling subjects on step 3 while subjects were continuing on P/R treatment, a two-step modeling was involved. In the first step, different means of the random intercepts and slopes by subjects' virologic response were allowed in the linear mixed effect model. If there was no significant difference in HRQOL profiles by subjects' SVR, the same means of the random intercepts and slopes by SVR were assumed in a more parsimonious model. In the linear mixed effects models for subjects on step 3 after they were off P/R treatment, the means of the random intercepts and random slopes were allowed to be different for subjects with SVR and non-SVR to examine possible different HRQOL profiles by subjects' SVR.

To evaluate the relationship within step between HRQOL and subjects' distress and depression level, linear mixed effects models were fit where the HRQOL was modeled as the outcome and distress or depression scores as covariates with random intercepts and random slopes. Associations were evaluated based on the estimated mean slopes from the linear mixed effects models.

All analyses were conducted at a 0.05 significance level without adjusting for multiplicity. The analyses were implemented in SAS V9.12 (SAS Institute Inc, Cary, NC).

RESULTS

Patients' demographic characteristics at enrollment

There were 329 subjects evaluated in step 1, 85 subjects in step 2 (including 3 who entered step 2 directly and 2 who failed to have an undetectable HCV RNA at week +36 on step 3 and enrolled in step 2) and 169 subjects in step 3. Table 1 summarizes the potential confounding variables by study steps. Other demographic characteristics for subjects enrolled in the study can be found in the report for the primary analysis for ACTG 5178 [2].

HRQOL of subjects while on lead-in P/R treatment (Step 1)

Table 3 summarizes HRQOL scores both at entry to step 1 and their changes over time by week. At entry to step 1 (Table 2), subjects without prior HCV treatment scored an average of 6.16 points lower in their social function score than those with prior HCV treatment ($p=0.02$). Female subjects scored an average of 8.85 points lower in their pain score than male subjects ($p=0.01$). There was a significant decrease in HRQOL over time, both in overall score and in all dimensions. The overall average HRQOL score decreased 6.26 points per week. Across all 8 dimensions of the HRQOL, average role function and energy level decreased by more than one point per week; social function score decreased by 0.98 point each week; and pain and Cognitive function scores decreased by 0.52 and 0.48 points per week respectively, with the slowest diminishing rate among the 8 dimensions of HRQOL.

HRQOL of subjects without EVR (Step 2: non-EVR)

Table 4 summarizes average HRQOL scores in non-EVR subjects both at entry to step 2 and their changes over time per week. At entry to step 2 (Table 2), gender was significantly related to physical function ($p=0.04$) and pain score ($p=0.04$). Female subjects scored an average of 13.16 points lower in their physical function score and 12.22 points lower in their pain score than males. Compared to white non-Hispanic subjects, Hispanic subjects scored an average of 24.22 points higher in their mental score. Although subjects without cirrhosis at study entry scored an average of 14.65 and 15.65 points higher in their social function score and physical function score compared to those with cirrhosis, there was no significant difference in any dimension of HRQOL with regard to subjects' cirrhosis status at entry to step 2. There were no significant changes in HRQOL scores over time for any dimension of the HRQOL score or the overall score. There were no significant differences in time effects between subjects continuing PEG-IFN compared to the placebo group.

HRQOL of subjects with EVR (Step 3: EVR)

Tables 5 and 6 summarize HRQOL scores in subjects with EVR both at entry to step 3 and changes over time per week while subjects continued on P/R and after they were off study treatment. At entry to step 3 (Table 2), prior HCV treatment was significantly related to the overall HRQOL, social function, cognitive function, mental and energy scores. HCV Treatment naïve subjects scored an average of 67.61, 10.65, 8.59, 8.32 and 11.83 points lower in the aforementioned HRQOL dimensions compared to treatment experienced subjects, respectively. Female subjects scored an average of 8.18, 12.82 and 13.28 units lower in social function, pain score and energy level than male subjects. In the analysis of HRQOL scores over time when subjects were continuing on P/R, the profile of HRQOL, both overall and all 8 dimensions, are not significantly different between those who were identified as having SVR 24 weeks after discontinuation of P/R and those who later were identified as non-SVR. The overall, general health status, role function and pain scores increased an average of 0.33 ($p=0.02$), 0.08 ($p=0.002$), 0.08 ($p=0.02$), and 0.07 ($p=0.01$) points weekly. During the 24-week off-treatment follow-up period, changes in the general

health and cognitive scores over time were significantly different between SVR and non-SVR subjects. Subjects with SVR had an average weekly increase of 0.45 units and 0.87 units in their general health and cognitive function over time, while the change of these scores over time in subjects without SVR was not significantly different from zero.

Association between HRQOL and symptom distress and depression levels

Table 7 summarizes the distress and depression levels at each step entry. At study entry the median (inter-quartile range, IQR) distress and depression (CES-D) scores are 17 (8, 29) and 24 (20, 27). After receiving PEG-IFN for 12 weeks, subjects showed increased distress and depression level regardless of their EVR status. At entry to step 2 (non-EVR) and step 3 (EVR), the median distress scores are 23.5 (13.5, 35) and 28 (17, 38). More subjects indicated having significant depressive symptoms, i.e., depression score ≥ 20 , with median (IQR) distress scores of 23 (18, 25) and 21 (16, 25) at entry to step 2 and step 3, respectively.

For subjects on step 1 and step 3, lower distress and depression levels were significantly related to higher values of HRQOL (all p-values $< .001$, Table 8). For subjects on step 2, the relationships between HRQOL and distress or depression levels were not significantly different between the treatment group and observational control group. Low depression levels were significantly related to high scores of role function (p-value = 0.006), social function (p-value $< .001$) and cognitive function (p-value $< .001$) of HRQOL. Distress levels were significantly negatively related to general health, physical function, pain score, mental health and energy level of HRQOL (p-values $< .001$). Although subjects' distress and depression level were correlated by the association analysis (results not shown), it is noteworthy that the distress level and depressive level were related to completely different dimensions of HRQOL for subjects without EVR, which may reflect differences in the survey instrument.

DISCUSSION

In recent years, there has been a growing interest in the evaluation of qualitative measures that are not captured routinely in HCV clinical trials. Though HRQOL is diminished in HCV/HIV compared to HIV mono-infection, the relationship between virologic response and HRQOL in HCV/HIV population is not reported, nor is the effect of long-term maintenance therapy [8–10].

In the present study, HCV/HIV coinfecting individuals receiving P/R experienced a significant decline in all HRQOL domains during the initial 12 weeks of therapy. This decline in HRQOL domains during P/R therapy, though previously unreported in HCV/HIV coinfection, has been observed and extensively described in HCV mono-infected individuals [11–15]. In contrast to the published findings in the latter population which show a decline in only some of the HRQOL domains, we observed a significant decrease in all domains measured. Furthermore, contrary to the HCV mono-infection studies, this study provides useful insights into the possible relationship between HRQOL and side effects of treatment. Though previous studies have postulated that the decline in HRQOL is due to the side effects of P/R, there has been no data to support this hypothesis. The findings of the current study attempt to fill this gap by providing data that shows a relationship between HRQOL and the side effects of P/R therapy.

The clinical tools used to measure side effects of P/R in this study were the symptom distress module, which determines the overall distress level, and CES-D scale, which evaluates depressive symptoms. We found a direct correlation between the side effects and the HRQOL during P/R therapy. The higher the depressive level and distress symptoms, the lower the HRQOL profile score. Interestingly, we observed a difference in the specific

HRQOL domains associated with depression and symptom distress for subjects without EVR. Depression significantly correlated with a decline in role, social and cognitive function, while symptom distress correlated with general health, physical function, pain score, mental health and energy levels. The reason for the difference in HRQOL domain affected by depression and symptom distress is unknown.

Though the liver is the primary reservoir for HCV, its clinical manifestations are not limited to the liver but include extrahepatic symptoms. These extrahepatic manifestations are well described and contribute to the overall morbidity of patients with HCV infection. Among these non-hepatic symptoms, the link between the presence of HCV and neuropsychologic deficits such as cognitive impairment has been extensively studied [16–18]. Most of these studies postulate that these symptoms correlate with the presence of HCV. Therefore an eradication of the virus may lead to resolution or improvement of these symptoms. In the current study, we found a significant improvement in HRQOL domains (general health and cognitive function) in recipients who had SVR compared to the non-SVR group. Though cognitive deficits are common in patients with either HCV or HIV, it is unclear if the prevalence is higher in those with HCV/HIV co-infection [19,20]. Furthermore, the impact of SVR on cognitive function in this population is unclear. The lack of information pertaining to the impact of P/R on cognitive dysfunction is in part related to the HRQOL instruments used to measure general health status in HCV clinical studies. The SF-36, which is the most widely HRQOL tool utilized in HCV studies, does not measure cognition. This is in contrast to the ACTG HRQOL questionnaire which includes items that specifically evaluate cognition. Therefore, this study provides unique information about the association between HCV and cognition in this population. Though some studies have raised concern over the impact of cirrhosis with hepatic encephalopathy on cognitive function among patients with HCV, in this study there was no correlation between cirrhosis and cognitive dysfunction [21–24]. Nevertheless, the added benefit of an improved cognitive function among those with SVR observed in this study, needs to be confirmed by formal neuropsychological tests.

The main objective of maintenance therapy was to determine if antiviral treatment with pegylated interferon for an extended period of time could slow liver disease progression in HCV/HIV coinfecting patients with chronic HCV. To date, the two large prospective clinical trials of maintenance therapy, HALT-C and SLAM-C failed to meet this clinical endpoint [2,25]. The HALT-C trial was for patients with HCV alone, while SLAM-C study enrolled patients with HCV/HIV co-infection. In the latter study, no significant change in HRQOL was observed over time in the HRQOL domains among either those on long-term pegylated interferon or subjects in the observational group. Furthermore, there was no difference in HRQOL between the subjects on long-term pegylated interferon compared to the observational group. This is contrary to the findings from HALT-C trial, which showed a significant decline in vitality and a trend towards a lower physical summary score in the treatment group compared to control [26]. Unfortunately, it is not possible to perform a head-to-head comparison of both studies due to the difference in patient population, dose of pegylated interferon and HRQOL questionnaire (SF-36) used.

In summary, patients with HCV/HIV coinfection that achieved SVR with P/R therapy demonstrated a significant improvement in HRQOL. However, no benefit was observed in patients that received maintenance therapy. Therefore in addition to the failure in ameliorating fibrosis progression, maintenance therapy had no beneficial effect on the HRQOL in this population.

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Table 1

Summary of potential confounding variables.

	Step 1		Step 2		Step 3	
	N	(%) [*]	N	(%) [*]	N	(%) [*]
prior HCV						
Yes	106	32.22	36	43.9	49	28.99
No	223	67.78	46	56.1	120	71.01
Gender						
Male	274	83.28	58	70.73	150	88.76
Female	55	16.72	24	29.27	19	11.24
Race						
White Non-Hispanic	142	43.29	24	29.63	88	52.07
Black Non-Hispanic	123	37.5	44	54.32	49	28.99
Hispanic	50	15.24	12	14.81	23	13.61
Asian, Pacific Islander	3	0.91	0	0.00	3	1.78
American Indian, Alaskan Native	4	1.22	0	0.00	2	1.18
More than one race	6	1.83	1	1.23	4	2.37
missing	1		4			
Cirrhosis at step1 entry (within 2 years)						
Yes	43	13.07	16	19.51	15	8.88
No	286	86.93	66	80.49	154	91.12
missing			3			
Cirrhosis at step2 entry (within 6 weeks)						
Yes			11	13.75		
No			69	86.25		
missing			5			

* Percentage of subjects with non-missing values;

Table 2

Baseline covariates that are significantly related to different dimensions of HRQOL, by step

Step entry	HRQOL	Covariate	value	Difference	s.e.	p-value
1	Social Function	Prior HCV treatment (Ref=Yes)	No	-6.16	2.62	0.019
	pain	Sex (Ref=M)	F	-8.85	3.49	0.012
2	Physical Function	Sex (Ref=M)	F	-13.16	6.38	0.042
	Pain	Sex (Ref=M)	F	-12.22	6.06	0.047
	Mental	Race (Ref=White non-Hispanic)	Black Non-Hispanic	6.00	5.16	0.249
3			Hispanic	24.22	7.04	0.001
			More than one race	13.94	20.06	0.489
	Social Function	Cirrhosis(Ref=Yes)	N	14.65	7.00	0.040
	Physical Function	Cirrhosis(Ref=Yes)	N	15.65	7.18	0.032
	Overall	Prior HCV treatment (Ref=Yes)	No	-67.61	27.18	0.014
	Social Function	Prior HCV treatment (Ref=Yes)	No	-10.65	4.43	0.017
	Cognitive Function	Prior HCV treatment (Ref=Yes)	No	-8.59	3.83	0.026
	Mental	Prior HCV treatment (Ref=Yes)	No	-11.83	3.85	0.003
	Energy	Prior HCV treatment (Ref=Yes)	No	-8.18	4.04	0.044

Table 3

HRQOL in subjects with lead-in P/R treatment (Step 1)

	N	Baseline		Changes over time by week		
		mean	s.e.	est	s.e.	p-value
Overall	320	579.8	142.36	-6.26	0.64	<.001
General Health	325	61.18	23.38	-0.68	0.11	<.001
Physical Function	328	72.41	26.52	-0.76	0.13	<.001
Role Function	327	79.51	27.00	-1.13	0.15	<.001
Social Function	328	80.72	22.31	-0.98	0.13	<.001
Cognitive Function	321	78.98	19.85	-0.48	0.10	<.001
Pain	328	73.02	23.84	-0.52	0.11	<.001
Mental	325	70.91	19.72	-0.60	0.10	<.001
Energy	325	64.22	23.34	-1.13	0.11	<.001

Table 4

HRQOL in non-EVR subjects (Step 2)

	<u>Baseline</u>		<u>Change over time by weeks</u>					
	N	mean	s.e.	<u>PEG-IFN</u>			<u>Observational control</u>	
				est	s.e.	p-value	est	p-value
Overall	78	524.85	151.50	-0.40	0.48	0.411	-0.58	0.45
General Health	80	52.76	24.00	-0.05	0.07	0.486	-0.04	0.07
Physical Function	81	66.20	25.80	0.02	0.09	0.792	-0.13	0.09
Role Function	83	69.58	30.00	0.03	0.10	0.739	-0.01	0.09
Social Function	83	76.09	25.14	-0.06	0.09	0.488	-0.13	0.08
Cognitive Function	80	74.67	21.83	-0.16	0.07	0.029	-0.06	0.07
Pain	83	67.84	24.84	-0.07	0.07	0.362	0.00	0.06
Mental	81	66.38	21.15	-0.13	0.08	0.131	-0.05	0.07
Energy	81	53.58	25.75	-0.09	0.09	0.319	0.02	0.08

Table 5

HRQOL in EVR subjects while on P/R (Step 3 on treatment)

	N	Baseline		Change over time by weeks		
		mean	s.e.	est	s.e.	p-value
Overall	78	524.85	151.50	0.33	0.15	0.024
General Health	80	52.76	24.00	0.08	0.02	0.002
Physical Function	81	66.20	25.80	0.02	0.03	0.490
Role Function	83	69.58	30.00	0.08	0.03	0.015
Social Function	83	76.09	25.14	0.02	0.03	0.514
Cognitive Function	80	74.67	21.83	-0.01	0.02	0.661
Pain	83	67.84	24.84	0.07	0.03	0.007
Mental	81	66.38	21.15	0.02	0.02	0.432
Energy	81	53.58	25.75	0.04	0.03	0.104

Table 6

HRQOL in EVR subjects while off P/R treatment (Step 3 off treatment)

	SVR			Non-SVR		
	est	s.e.	p-value	est	s.e.	p-value
Overall	1.22	5.65	0.830	-0.52	6.17	0.933
General Health	0.45	0.13	0.002	-0.13	0.15	0.367
Physical Function	0.25	0.24	0.302	0.17	0.13	0.202
Role Function	0.24	0.26	0.368	0.04	0.19	0.839
Social Function	0.27	0.25	0.291	-0.15	0.17	0.400
Cognitive Function	0.87	0.34	0.015	-0.13	0.19	0.515
Pain	-0.13	0.23	0.571	0.11	0.14	0.448
Mental	0.15	0.14	0.308	-0.16	0.13	0.216
Energy	0.16	0.35	0.659	-0.33	0.38	0.395

Table 7

Distress and depression levels at entry to each step

Entry to Steps	Distress			Depression		
	N	Mean(std)	Median(Q1, Q3)	N	Mean(std)	Median(Q1, Q3)
1	319	19.60 (14.37)	17 (8, 29)	328	22.80 (5.19)	24 (20, 27)
2	80	25.84 (15.91)	23.5 (13.5, 35)	83	20.96 (5.89)	23 (18, 25)
3	162	28.53 (15.18)	28 (17, 38)	163	20.34 (6.07)	21 (16, 25)

Table 8

Correlation of HRQOL with distress and depression level based on mixed effect model

Step	Outcome	Distress level			Depression Level		
		Estimate	s.e.	P-value	Estimate	s.e.	P-value
1	Overall	-7.68	0.27	<.001	19.20	0.72	<.001
	General Health	-0.94	0.05	<.001	2.46	0.14	<.001
	Physical Function	-0.96	0.06	<.001	2.14	0.16	<.001
	Role Function	-1.05	0.07	<.001	2.57	0.19	<.001
	Social Function	-1.05	0.05	<.001	2.86	0.14	<.001
	Cognitive Function	-0.85	0.05	<.001	2.33	0.11	<.001
	Pain	-0.90	0.05	<.001	1.72	0.15	<.001
	Mental	-0.79	0.05	<.001	2.62	0.10	<.001
	Energy	-1.12	0.05	<.001	2.63	0.13	<.001
2	Overall	-6.56	6.06		12.34	26.59	
	PEG-IFN	-4.78	6.12	0.415	12.19	27.16	0.812
	Control						
	General Health	-0.95	0.16	<.001	1.55	8.52	0.972
	PEG-IFN	-0.94	0.12		1.35	8.72	
	Control						
	Physical Function	-0.83	0.14	<.001	1.46	5.23	0.946
	PEG-IFN	-0.98	0.13		0.99	5.35	
	Control						
	Role Function	-1.05	1.69	0.818	1.20	0.51	0.006
	PEG-IFN	-0.23	1.73		1.24	0.53	
	Control						
	Social Function	-0.84	1.13	0.586	2.38	0.38	<.001
	PEG-IFN	-0.84	1.15		2.23	0.40	
	Control						
	Cognitive Function	-0.66	0.92	0.725	1.97	0.37	<.001
	PEG-IFN	-0.33	0.93		2.19	0.26	
	Control						
	Pain	-0.86	0.14	<.001	1.10	9.79	0.988
	PEG-IFN	-0.84	0.13		1.11	10.02	
	Control						
	Mental	-0.77	0.13	<.001	2.39	4.09	0.749
	PEG-IFN	-0.80	0.11		2.05	4.19	
	Control						
	Energy	-1.02	0.14	<.001	1.36	5.50	0.937
	PEG-IFN	-0.97	0.15		1.47	5.62	
	Control						

Step	Outcome	Distress level			Depression Level		
		Estimate	s.e.	P-value	Estimate	s.e.	P-value
3	Overall	-7.68	0.27	<.001	16.05	0.71	<.001
	General Health	-0.94	0.05	<.001	2.21	0.13	<.001
	Physical Function	-0.96	0.06	<.001	1.84	0.15	<.001
	Role Function	-1.05	0.07	<.001	2.26	0.17	<.001
	Social Function	-1.05	0.05	<.001	2.67	0.14	<.001
	Cognitive Function	-0.85	0.05	<.001	1.93	0.12	<.001
	Pain	-0.90	0.05	<.001	1.44	0.15	<.001
	Mental	-0.79	0.05	<.001	2.43	0.12	<.001
	Energy	-1.12	0.05	<.001	2.19	0.12	<.001