Peginterferon With or Without Ribavirin Has Minimal Effect on Quality of Life, Behavioral/Emotional, and Cognitive Outcomes in Children

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The aim of this study was to prospectively assess the quality of life (QOL), behavioral/emotional functioning, and cognitive status of children undergoing treatment for hepatitis C virus (HCV) infection. In all, 114 children (5 to 18 years old) enrolled in a multisite randomized clinical trial (Peds-C) to evaluate peginterferon alpha 2a (PEG 2a) with ribavirin (RV) or with placebo (PL) completed several standardized measures prior to treatment and at 24 weeks, 48 weeks, 6 months following treatment, and at two annual follow-up visits. After 24 weeks of treatment, mean physical QOL scores declined significantly for both groups from baseline to 24 weeks of treatment ($F = 5.8$, $P = 0.004$), although scores remained in the average range. There were no significant time or group effects for behavioral/emotional or cognitive functioning. Three children (5%) in the PEG 2a + RV group and no children in the PEG 2a + PL group had a clinically significant increase in depression symptoms. For those children who received 48 weeks of treatment, there were no significant time or group effects on any of the outcome measures ($P > 0.05$). A majority of children in both the PEG 2a + RV and PEG 2a + PL groups experienced no clinically significant change in physical QOL, behavioral adjustment, depression, or cognitive functioning during or after treatment. Conclusion: Overall QOL and psychosocial functioning are not deleteriously impacted by PEG 2a + RV or PL treatment of children with HCV. (HEPATOLOGY 2011;53:1468-1475)

In the United States, an estimated 23,000 to 43,000 children are infected with hepatitis C virus (HCV), with 7,200 new cases annually.[1] Although the course of HCV infection in children is generally more benign than that seen in adults, ≈30% of infected children will develop symptomatic or progressive disease and be at risk for cirrhosis and hepatocellular carcinoma later in life.[2-4] However, there is emerging evidence that chronic HCV treatment in children and adolescents can yield virologic results comparable to, or even better than, those in adults.[5-7] For instance, in the largest randomized controlled trial

to date, Schwarz et al. and the Peds-C Clinical Research Network[5] showed that peginterferon alfa-2a (PEG 2a) plus ribavirin (RV) is superior to PEG 2a plus placebo (PL) for chronic HCV in children and adolescents. Sustained virologic response (SVR) was achieved for 53% of the 55 children who received PEG 2a + RV, in comparison to 21% of the 59 children randomized to PEG 2a + PL.

The chronic HCV literature is replete with findings of quality of life (QOL), psychological, and cognitive deficits in treatment-naïve adults as well as those receiving interferon and ribavirin therapy.[8-17] However, comparatively less is known about how HCV and its treatment affects these clinical parameters in children. Nydegger et al.[18] reported on a small group of children who acquired HCV in the first year of life who had lower QOL compared to noninfected children. In contrast, baseline data from the Peds-C study showed that treatment-naive children with HCV do not manifest global impairment in QOL, cognitive, behavioral, or emotional functioning.[19] Iorio et al.[20] published one of the only prospective studies examining QOL in children undergoing treatment for chronic HBV and HCV infection. They showed that, whereas tolerability was not a limiting factor in interferon-alpha treatment in children, QOL deteriorated significantly during treatment and did not return to baseline until ≈3 months after stopping treatment. They noted three- to four-fold increases in irritability and all the psychosocial dimensions of the Sickness Impact Profile (e.g., Social Interaction, Emotional Behavior, Alertness Behavior) during treatment. This finding suggests that significant QOL morbidity may accompany interferon-alpha treatment in children as it does in adults.

Although QOL is emerging as an important endpoint in pediatric clinical trials of HCV treatments, there is a paucity of data on other patient-oriented outcomes that are pertinent to child development and function. The inclusion of patient-oriented outcomes such as behavioral adaptation, depression, anxiety, and cognitive functioning in HCV pediatric clinical trials is important for several reasons. The impact of HCV treatments on these parameters in children is not presently known and such information will allow health professionals to better inform patients and their parents about the range of possible side effects. Also, identifying the complete range of morbidity associated with chronic HCV and its treatments may facilitate the development and implementation of psychotherapeutic or psychopharmacological interventions aimed at attenuating morbidity in these children.

The aim of this study was to prospectively assess the QOL, behavioral/emotional functioning, and cognitive status of children participating in the Peds-C study.[5] As part of this multisite randomized controlled clinical trial evaluating the differential effect of PEG 2a + RV versus PEG 2a + PL, children and their parents participated in an extensive psychosocial assessment protocol at multiple timepoints. We hypothesized, based on findings in the adult literature on interferon-based treatments, that children in both study arms would report worsening QOL, behavioral/emotional functioning, and cognitive functioning relative to their baseline (pretreatment) level of functioning.

Patients and Methods

Eligible study participants were 5 to 18-year-old children with documented HCV viremia on two tests ≥6 months apart and/or one positive test in a child with maternal-fetal transmission, chronic hepatitis consistent with HCV infection on liver biopsy within 36 months of screening, and compensated liver disease (Child-Pugh Grade A clinical classification). Exclusion criteria were any prior treatment with interferon or ribavirin, decompensated liver disease, major depression, or history of other severe illness. Written informed consent was obtained from the child's parent or guardian, and children over 12 years old provided written assent.

Development and implementation of the Peds-C study design has been described elsewhere (www.clinicaltrials.gov).[5,21] In brief, this was a multisite study in which enrolled participants were randomized (stratified by site according to HCV genotype) to receive either PEG 2a + RV or PEG 2a + PL. Children received PEG 2a subcutaneously once weekly (180 μg/1.73 m^2 body surface area) plus either RV administered orally on a daily basis (15 mg/kg) or placebo tablets. Virologic response was assessed after the first 24 weeks of treatment. For children with undetectable HCV RNA, treatment continued in their originally assigned group for an additional 24 weeks, thus resulting in 48 total weeks of therapy. For children with detectable HCV RNA in the PEG 2a + RV arm, treatment was stopped and they were considered nonresponders. For children with detectable HCV RNA in the PEG 2a + PL arm, they were also considered nonresponders but were offered "open label" PEG 2a + RV therapy for 48 weeks (although treatment was terminated if HCV RNA was detected after 24 weeks).

Measures of QOL, behavioral/emotional, and cognitive functioning were obtained for all children at baseline (pretreatment) and at 24 weeks, 48 weeks, 6 months following treatment, and at two subsequent annual visits. A detailed description of the rationale for

measurement selection and implementation is published elsewhere.[21]

Quality of Life. QOL was assessed using the Child Health Questionnaire (CHQ) — Parent Form 50,[22] a standardized measure of functional status and well-being for children 5 to 18 years old that is completed by the child's parent or guardian. The CHQ yielded two composite scores for physical health and psychosocial functioning, as well as scores for 11 different scales: physical functioning, role/social limitations (emotional, physical), general health, bodily pain/discomfort, parent impact (emotional, time), self-esteem, mental health, general behavior, and family impact. Parents answered questions based on their perceptions of the child's QOL over the past 4 weeks. Scores range from 0-100, with higher scores reflecting better QOL. T-scores ≤40 on the Physical Summary and Psychosocial Summary composite measures are considered indicative of clinical impairment in QOL. As described,[21] a self-report version of the CHQ was administered to children 10 years and older. However, there was more variability in its completion over time compared to the parent version, and the correspondence between parent- and child-report versions is the focus of a separate analysis and article.

Behavioral/Emotional. The Child Behavior Checklist (CBCL)[23] was used to assess behavioral functioning and was completed by the child's parent or guardian. It yielded scores for three composite scales (Internalizing, Externalizing, and Total Behavior Problems) and eight clinical scales: Anxious/Depressed, Withdrawn/Depressed, Somatic Problems, Social Problems, Thought Problems, Attention Problems, Rule-Breaking Behavior, and Aggressive Behavior. Raw scores were converted to T-scores, with a mean of 50 and standard deviation (SD) of 10. Higher scores reflect more behavioral or emotional problems. T-scores ≥ 65 are considered indicative of clinically significant behavior problems. Although the CBCL was validated in children 6 to 18 years old, we used it in the current study for children as young as 5 years old to assess symptoms (e.g., social problems, thought problems) that are not part of the CBCL preschool version.

The Children's Depression Inventory (CDI)[24] was completed by the child and it assessed affective, cognitive, and behavioral symptoms of depression. A total score ≥19 is indicative of possible clinical depression. The CDI was administered at every patient visit to screen for depression. If the CDI score was ≥19, then the site investigator interviewed the child to further assess for clinical depression. If the child met criteria for major depression, s/he was referred to a mental health professional for further assessment and treatment. Study medications were discontinued if symptoms did not improve within 8 weeks of initiation of treatment for depression or if other significant symptoms developed (e.g., substance abuse, recent suicide attempt or current suicidal ideation with a plan, psychosis, bipolar disorder, or inability of family to monitor child's safety).

Cognitive Functioning. Cognitive functioning was measured using the Behavior Rating Inventory of Executive Function (BRIEF).[25] The BRIEF is a parent-report measure of executive functioning in children ages 5 to 18 years. It includes two broad indices (Behavioral Regulation, Metacognition) and eight clinical scales (Inhibit, Shift, and Emotional Control, Initiate, Working Memory, Plan/Organization, Organization of Materials, Monitor), and a Global Executive Composite score. Raw scores were converted to T-scores (mean = 50, SD = 10), with higher scores reflecting more cognitive impairment. T-scores ≥65 are considered indicative of clinical impairment in executive function.

The study protocol was approved by the Institutional Review Boards at all study sites. An independent, external data and safety monitoring board (DSMB) appointed by and advisory to the National Institute of Diabetes and Digestive and Kidney Diseases reviewed and approved the study design and monitored its conduct.

Statistical Analysis. Descriptive statistics were calculated to summarize the medical, sociodemographic, and outcome variables. Because children who did not respond to PEG 2 a + PL after 24 weeks were offered "open label" PEG 2a + RV therapy, a multilevel approach to analysis was necessary. In the first set of analyses, we included all children as originally randomized to examine the effect of treatment group over the first 24 weeks of therapy prior to the first treatment decision point. We used repeated measures analyses of variance to assess treatment group and time effects on all outcomes. We then classified children into three groups based on clinical decline, improvement, or no change in scores from baseline to 24 weeks. Clinical decline was operationalized as a >1 SD change in score plus a change in score classification from no impairment at baseline to clinical impairment at 24 weeks. Clinical improvement was defined as >1 SD change in score plus a change in score classification from clinical impairment at baseline to no impairment at 24 weeks. In the second set of analyses, we used only those children with nondetectable HCV RNA at the 24-week assessment to examine whether continuation of the assigned treatment for an additional 24 weeks differentially impacted children by group assignment over time. We used repeated measures analyses
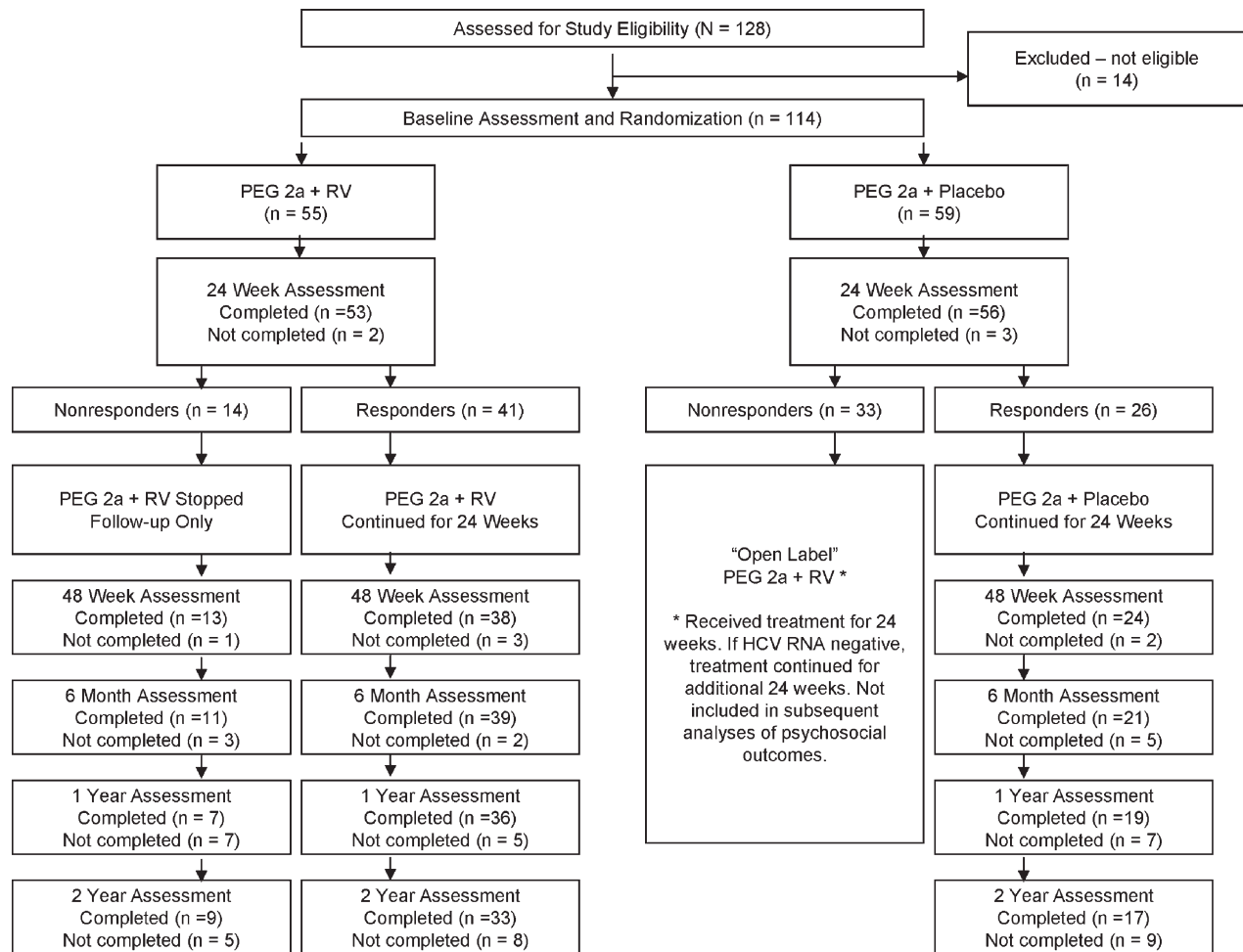
Fig. 1. CONSORT diagram showing patient progression through the study.

of variance to examine for main and interaction effects over time. Clinically significant decline/improvement in functioning was again examined as noted above. To reduce the probability of Type I error rate, analyses initially were performed only on the composite or summary scales of the outcome measures. If a statistically significant main or interaction effect emerged, we examined for differences on the individual scales for the respective outcome measure. In the final set of analyses, we calculated Pearson correlation coefficients and T tests to examine the relationship between sociodemographic characteristics and outcomes at the different timepoints. Due to the large number of tests in this analysis cluster, we considered $P < 0.01$ as the level of statistical significance. PAWS (v. 17.0) statistical software was used for all analyses.

Results

Sample Characteristics

Figure 1 illustrates participant progression through the study. Participants were 114 children who met study eligibility criteria. Fifty-five children were randomized to the PEG 2a + RV group and 59 children were randomized to the PEG 2a + PL group. There were no significant differences between the two groups on baseline sociodemographic or medical characteristics (Table 1). The total sample had a mean age of 10.7 years (range 5 to 17), 75% was white, 45% was female, and 81% had HCV genotype 1.

All Children: Baseline to 24 Weeks

Table 2 displays the means and SDs for the composite or summary scores for each outcome measure by treatment group.

Quality of Life. There was a significant time main effect for the CHQ Physical Summary score ($F = 5.81$, $P = 0.004$), but no significant effect for treatment group or significant time by treatment group interaction effect. The mean Physical Summary score declined significantly from baseline (51.7 $\pm$ 6.0) to the 24 week assessment (49.4 $\pm$ 8.1), although both means were within the average range. Individual CHQ

Table 1. Baseline Characteristics by Treatment Group and for the Total Sample

Characteristic		PEG 2a + RV (n = 55)	PEG 2a + PL (n = 59)	Total Sample (N = 114)
Age, yrs		10.7 ± 3.3	10.8 ± 3.6	10.7 ± 3.4
	5 - 11	30 (54%)	30 (51%)	60 (53%)
	12 - 18	25 (46%)	29 (49%)	54 (47%)
Gender	Male	27 (49%)	36 (61%)	63 (55%)
	Female	28 (51%)	23 (39%)	51 (45%)
Race	White	43 (78%)	42 (71%)	85 (75%)
	Black / African American	1 (2%)	4 (7%)	5 (4%)
	Asian	3 (6%)	2 (3%)	5 (4%)
	American Indian / Alaska Native	1 (2%)	0 (0%)	1 (1%)
	More than one race	1 (2%)	5 (9%)	6 (5%)
	Unknown	6 (11%)	6 (10%)	12 (11%)
HCV genotype	1	45 (82%)	47 (80%)	92 (81%)
	2	4 (7%)	3 (5%)	7 (6%)
	3	6 (11%)	7 (12%)	13 (11%)
	6	0 (0%)	2 (3%)	2 (2%)
Transmission mode	Maternal-infant	39 (71%)	47 (80%)	86 (75%)
	Transfusion	6 (11%)	2 (3%)	8 (7%)
	Other	10 (19%)	10 (18%)	20 (18%)
Estimated duration of infection, mos.		105 ± 56	111 ± 55	108 ± 55
ALT (IU/L)		49 ± 59	49 ± 59	49 ± 59

Treatment groups did not differ significantly on any characteristic (all $P > 0.05$).

scale analysis showed that there was a statistically significant decrease (worsening) in Bodily Pain (82.9 ± 18.5 versus 74.5 ± 23.0, $P < 0.001$) and General Health (66.6 ± 15.3 versus 63.3 ± 18.1, $P = 0.02$) scores from baseline to 24 weeks. Eight (15%) children in the PEG 2a + RV group and five (9%) children in the PEG 2a + PL group had a clinically significant decline in physical QOL between baseline and 24 weeks (Table 3). Four (7%) children in the PEG 2a + RV and three (5%) in the PEG 2a + PL group had a clinically significant decline in psychosocial QOL.

Behavioral/Emotional. There were no significant effects for time, treatment group, or time by treatment group interaction for the CBCL Internalizing, Externalizing, or Total Behavior Problems scores or for the CDI Total score ($P > 0.05$). Six (3 PEG 2a + RV, 3 PEG 2a + PL) and three (all PEG 2a + RV) children had clinically significant worsening of internalizing and externalizing behaviors, respectively, between baseline

and 24 weeks (Table 3). Examination of CDI scores showed that three (5%) children in the PEG 2a + RV group and no children in the PEG 2a + PL group experienced a clinically significant increase in depression symptoms from baseline to 24 weeks. One child in the PEG 2a + RV group was withdrawn from treatment due to a suicidal gesture and subsequent hospitalization, and one child in the PEG 2a + PL group was withdrawn from the study due to an increase in aggressive behaviors.

Cognitive Functioning. There were no significant effects for time, treatment group, or time by treatment group interaction for the BRIEF composite scores ($P > 0.05$). Three children receiving PEG 2a + RV had significant clinical deterioration in their Global Executive functioning from baseline to 24 weeks (Table 3). No children other than the two noted above were removed from the study due to changes in cognitive or neuropsychological functioning.

Table 2. Means ± Standard Deviations for Primary Outcomes at Baseline and 24 Weeks by Treatment Group, N = 114

Measure	PEG 2a + RV (n = 55)		PEG 2a + PL (n = 59)	
	Baseline	24 Weeks	Baseline	24 Weeks
CHQ Physical Summary	52.1 ± 4.8	49.8 ± 7.5	51.1 ± 7.1	49.0 ± 8.6
CHQ Psychosocial Summary	52.1 ± 7.9	52.3 ± 10.2	50.1 ± 10.4	52.2 ± 7.8
CBCL Internalizing	52.4 ± 8.5	51.0 ± 11.0	52.2 ± 10.9	50.1 ± 11.0
CBCL Externalizing	50.4 ± 9.4	48.8 ± 10.3	50.0 ± 10.4	48.5 ± 9.9
CBCL Total Behavior Problem	51.5 ± 9.3	49.7 ± 10.2	50.6 ± 11.6	48.2 ± 11.1
CDI Total Score	5.9 ± 4.2	6.2 ± 5.6	5.9 ± 4.6	5.1 ± 3.1
BRIEF Global Executive Composite	53.5 ± 9.9	52.2 ± 10.1	53.7 ± 12.0	51.6 ± 9.6

Abbreviations: CHQ = Child Health Questionnaire; CBCL = Child Behavior Checklist; CDI = Child Depression Inventory; BRIEF = Behavior Rating Inventory of Executive Function.

Table 3. Number (%) of Children in Each Treatment Group with Clinical Improvement, Clinical Decline, or No Clinical Change After 24 weeks of Treatment, N = 114

Measure	PEG 2a + RV (n = 55)			PEG 2a + PL (n = 59)		
	Improved	Declined	No Change	Improved	Declined	No Change
CHQ Physical Summary	0 (0%)	8 (15%)	47 (86%)	3 (5%)	5 (9%)	51 (86%)
CHQ Psychosocial Summary	3 (5%)	4 (7%)	48 (88%)	5 (9%)	3 (5%)	51 (86%)
CBCL Internalizing	2 (4%)	3 (5%)	50 (91%)	4 (7%)	3 (5%)	52 (88%)
CBCL Externalizing	1 (2%)	3 (5%)	51 (93%)	2 (3%)	0 (0%)	57 (97%)
CBCL Total Behavior Problem	1 (2%)	2 (4%)	52 (94%)	3 (5%)	2 (3%)	54 (92%)
CDI Total Score	0 (0%)	3 (5%)	52 (95%)	2 (3%)	0 (0%)	57 (97%)
BRIEF Global Executive Composite	3 (5%)	3 (5%)	49 (90%)	3 (5%)	0 (0%)	56 (95%)

Abbreviations: CHQ = Child Health Questionnaire; CBCL = Child Behavior Checklist; CDI = Child Depression Inventory; BRIEF = Behavior Rating Inventory of Executive Function.

Children with Nondetectable HCV RNA Who Received 48 Weeks of Treatment

At the 24 week assessment, 41 children in the PEG 2a + RV group and 26 children in the PEG 2a + PL group had nondetectable HCV RNA and continued treatment in their original randomized condition for an additional 24 weeks. Table 4 presents the means and SDs for the outcome measures for this subsample of children. Repeated measures analyses of variance showed that there were no statistically significant time, treatment group, or time by treatment group effects for any of the outcome measures during the 48 weeks of treatment or at the 6-month follow-up assessment ($P > 0.05$).

Among the 41 children who continued on PEG 2a + RV therapy, 34 (83%) experienced no clinically significant change in physical QOL during treatment. Two (5%) children experienced a clinical decline in physical QOL at 24 weeks but returned to baseline levels by the end of treatment, and five (12%) experienced an early clinical decline that persisted through the end of treatment. However, three of these five children returned to baseline QOL levels by the 6-month posttreatment assessment. Most children experienced no

clinically significant change in internalizing behaviors (95%), externalizing behaviors (95%), or total behavior problems (93%) during the 48 weeks of treatment. On the CDI, two children (5%) had a clinically significant increase in depression symptoms during treatment. One child was removed from the study (as noted above) and the other child's symptoms remitted by the end of treatment. Finally, one child experienced a clinically significant decline in executive functioning at 24 weeks, which persisted through the duration of treatment and the 6-month follow-up assessment.

Of the 26 children who continued on PEG 2a + PL for 48 weeks, 21 (81%) did not have any clinically significant decline in physical QOL. Three (12%) children experienced a clinical decline in physical QOL at 24 weeks but returned to baseline levels by the end of treatment. Only one (4%) child had an early clinical decline that persisted through the end of treatment but this returned to baseline level after treatment was terminated. The majority had no significant clinical change in internalizing (77%), externalizing (92%), or total behavior problems (88%) during treatment. None of the children in this group had a clinically significant increase in depression symptoms (CDI) or

Table 4. Means ± Standard Deviations for Primary Outcomes at Baseline, Mid-Treatment (24 Weeks), Treatment End (48 Weeks), and First Follow-Up (6 Months) for Children with Nondetectable HCV RNA at 24 Weeks Who Continued Their Originally Assigned Treatment for an Additional 24 Weeks, n = 67

	PEG 2a + RV (n = 41)				PEG 2a + PL (n = 26)			
	Baseline	24 Weeks	48 Weeks	6 Months	Baseline	24 Weeks	48 Weeks	6 Months
CHQ Physical Summary	52.5 ± 4.2	49.3 ± 7.6	50.7 ± 8.0	51.9 ± 7.5	50.2 ± 7.6	47.2 ± 10.4	48.8 ± 9.3	51.8 ± 8.1
CHQ Psychosocial Summary	52.3 ± 8.1	52.0 ± 9.3	51.9 ± 8.4	52.9 ± 9.3	53.2 ± 7.9	51.2 ± 6.3	50.7 ± 10.6	52.9 ± 7.6
CBCL Internalizing	53.9 ± 8.4	50.9 ± 11.3	49.7 ± 10.4	49.1 ± 10.8	51.3 ± 11.3	51.6 ± 10.5	54.3 ± 14.5	51.8 ± 7.6
CBCL Externalizing	51.9 ± 9.0	49.9 ± 9.9	49.4 ± 9.5	48.5 ± 10.5	49.4 ± 9.8	48.8 ± 9.3	50.7 ± 10.4	51.6 ± 11.0
CBCL Total Behavior Problem	52.8 ± 8.5	50.4 ± 10.1	50.0 ± 10.3	48.5 ± 11.9	49.8 ± 9.9	50.1 ± 9.7	51.7 ± 13.5	51.5 ± 9.7
CDI Total Score	6.2 ± 4.4	6.1 ± 5.0	5.7 ± 3.8	4.7 ± 3.3	5.9 ± 4.5	5.1 ± 3.2	5.6 ± 4.1	6.9 ± 7.3
BRIEF Global Executive Composite	53.1 ± 10.5	52.5 ± 9.7	52.4 ± 12.1	51.8 ± 11.1	51.0 ± 11.5	51.4 ± 9.3	51.9 ± 10.4	52.0 ± 10.9

Abbreviations: CHQ = Child Health Questionnaire; CBCL = Child Behavior Checklist; CDI = Child Depression Inventory; BRIEF = Behavior Rating Inventory of Executive Function.

executive functioning problems (BRIEF) during 48 weeks of treatment or the 6-month follow-up period.

Long-Term Follow-Up

For all children who completed 48 weeks of treatment, scores on all outcome measures obtained at the 1-year and 2-year follow-up assessments did not differ significantly from baseline scores ($P > 0.05$). Very few children had clinical elevations on the CBCL, no child had a clinically high depression score at 1 year, and only one child (PEG 2a + RV) had a clinically elevated depression score at the 2-year follow-up assessment.

Relationship Between Sociodemographic Characteristics and Outcomes

Age, gender, race, transmission mode, and baseline alanine aminotransferase (ALT) were not significantly associated with QOL, behavioral/emotional, or cognitive outcomes at any time.

Discussion

A sustained virologic response, defined by undetectable serum HCV RNA 24 weeks after treatment cessation, is the primary objective of chronic HCV treatment. However, the virologic benefits of HCV treatment may be attenuated by negative changes along other clinical parameters that are of importance to patients and their caregivers, including QOL and psychological functioning. For instance, compromised QOL, fatigue, and depression increases the likelihood that adults will discontinue HCV treatment before realizing health benefits.[8,17,26] Findings from the current study, however, indicate that few children experience clinically significant changes in QOL, behavior problems, depression, or cognitive functioning during or after HCV treatment. Previously, we reported that pretreatment scores for this HCV pediatric cohort were comparable to that of healthy children,[19] and now we provide evidence that this remains largely unchanged after 48 weeks of peginterferon with ribavirin (or placebo) treatment and for 2 years after cessation of therapy. As the first randomized pediatric study to examine the QOL, psychological functioning, and cognitive impact of both peginterferon alone and with ribavirin, these findings have important clinical implications.

Overall QOL, behavior, depression, or executive function did not change for children over time, regardless of whether they received PEG 2a + RV or PEG 2a + PL. On the surface, this finding differs from both pediatric and adult studies, which have reported declines in QOL and other functional or psychological

parameters during HCV treatments.[20,27] For instance, whereas PEG 2a has fewer QOL side effects than unmodified interferon,[28,29] the addition of RV has been shown to substantially impair QOL in adults.[27] Relative to adults, children may have less severe disease, fewer medical and psychiatric comorbidities, and more available and stable social support systems. These factors may account for the lower incidence of QOL and behavioral/emotional impairment observed in the current study.

Iorio et al.[20] showed that the QOL of children deteriorates in the first month of interferon-alpha treatment, although QOL returned to baseline within 3 months of concluding treatment. We did not conduct QOL assessments during the first 6 months of treatment, so we are unable to determine whether impairments were present in our cohort during the early part of treatment. However, we did find that, for the few children who experienced clinically significant changes in QOL and behavioral/emotional functioning, almost all of them returned to healthy baseline levels by the end of treatment or by the 6-month follow-up assessment. It is important to note the different methodological and treatment characteristics between our study and the Iorio et al. study when evaluating these findings. For instance, in contrast to our study, the Iorio et al. study included children with different viral infections (HBV and HCV) and treated with various interferon types, schedules, and routes of administration. Also, Iorio et al. measured QOL using a modified version of the Sickness Impact Profile (SIP), which is an adult-based health status measure that has not been standardized on pediatric samples. In contrast, our patient cohort was homogeneous, children received a standardized antiviral regimen, and we used QOL instruments that have been developed and validated specifically for pediatric populations.

Findings reported herein must be considered in the context of several important study limitations. First, we present data based primarily on parent or guardian report. Such reports can be biased for many different reasons and, therefore, may not accurately capture the true functional status of the child. For instance, parents who are more stressed and worried about their child's medical status may respond different to questions about their child's functioning, compared to parents who are coping well with their child's condition. Second, although the sample size was large compared to published literature, the number of children who remained in their assigned treatment through the full 48 weeks of treatment was relatively small and this may have limited our ability to detect small changes in

QOL functioning over time. Third, we did not assess QOL and the other psychosocial outcomes until 24 weeks after treatment initiation. It is possible that changes in these parameters occurred in the early stages of treatment and subsequently recovered by the time of our 24-week assessment.

In conclusion, PEG 2a + RV has been shown to be superior to PEG alone in achieving early and sustained virologic response in children and adolescents.[5] Data from the current study show that overall QOL, behavioral/emotional functioning, and cognitive functioning are not deleteriously impacted by the inclusion of RV. Nevertheless, because some individual children may experience clinical changes over time, we recommend close monitoring of these patient-oriented outcomes for those children receiving PEG 2a, with or without RV.

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