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The Combination of Ribavirin and Peginterferon Is Superior to Peginterferon and Placebo for Children and Adolescents Chronic Hepatitis C

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Abstract

Background & Aims—Although randomized trials of adults infected with hepatitis C virus (HCV) have shown that ribavirin increases efficacy of pegylated interferon (PEG), such trials have not been performed in children. We conducted a randomized, controlled trial of PEG and ribavirin, compared with PEG and placebo, in children 5–17 years old with chronic hepatitis C.

Methods—HCV RNA-positive children from 11 university medical centers were randomly groups assigned to receive either the combination of peginterferon alfa-2a (PEG 2a; 180 μg/1.73 m^2 body surface area, subcutaneously each week; n=59) and ribavirin (15 mg per kilogram orally in 2 doses daily) or PEG2a and placebo for 48 weeks (n=55). The primary endpoint was sustained virologic response (SVR, lack of detectable HCV RNA at least 24 weeks after stopping therapy).

Results—An SVR was achieved in 53% of children treated with PEG 2a and ribavirin, compared with 21% of children who received PEG 2a and placebo (P<0.001). Early virologic response (> 2 $\log_{10}$ IU reduction in HCV RNA at 12 weeks) had a negative predictive value of only 0.89 in children with genotype 1, indicating that these children might benefit from 24 weeks of therapy before stopping treatment. Side effects, especially neutropenia, led to dose modification in 40% of children. Eighty-two percent of the PEG/ribavirin and 86% of the PEG/placebo group were in

compliance with the year-2 follow-up visit; the durability of virologic response was 100% in both groups.

Conclusions—The combination of PEG and ribavirin is superior to PEG and placebo as therapy for chronic hepatitis C in children and adolescents.

Keywords

antiviral therapy; pediatric liver disease; multi-center pediatric trial

Introduction

Recently published data regarding the prevalence of chronic HCV infection in children in the United States (US) have called attention to this important public health problem. In the 3rd National Health and Nutrition Evaluation Survey, the prevalence of antibody to HCV among children and adolescents was 0.2 to 0.4% for an overall estimate of 132,000 antibody-positive children (1). More recent US census results have indicated 23,048 to 42,296 children are chronically infected with HCV, and that 7,200 new cases occur annually (2). In one study of infants infected with HCV at birth, 20% recovered, 50% developed mild asymptomatic chronic infection and 30% developed progressive disease (3).

Although chronic hepatitis C appears to run a more benign course in children compared to adults (4), significant histological liver disease can occur (5). Although rare, liver transplantation may be needed during adolescence (6) and cirrhosis may progress to hepatocellular carcinoma in the second decade of life (7). Treatment of chronic hepatitis C in adults has evolved from alpha interferon alone to the combination of interferon with ribavirin, and most recently, to the combination of PEG with RV. A beneficial response is defined as clearance of detectable serum or plasma HCV RNA during therapy with a sustained absence of the viral RNA for at least 6 months after stopping treatment. Response rates vary by viral genotype, from 40–50% among patients with genotype 1 (representing 60–70% of U S patients) to 70–80% among patients with genotypes 2 or 3 (20–30% of patients) (8).

Recommendations for treatment for HCV infection in children have been derived from trials in adults, although the efficacy and safety of these therapies may be different in children. The use of different treatment regimens in small, uncontrolled, clinical trials of thrice weekly interferon for chronic hepatitis C in children makes direct comparisons to adults difficult. However, reported sustained responses are better in children (30–60%) than adults (8–35%) (9). Addition of RV to interferon increased sustained response rates in adults to 30–40% (10). Studies in children have shown that standard interferon and RV yield response rates better than those in adults with fewer side effects (11)(12). These improved response rates in children may be secondary to the somewhat higher interferon dose in children ($3MU/m^2$)(11)(12) as opposed to that used in treating adults ($3MU/1.73m^2$)(10), to the generally lower viral load in children, relatively mild liver disease and/or other factors.

This combination therapy, which resulted in an SVR of 46% (54/118 children) in a large multi-center pediatric study (11) is now FDA-approved for children 3 years and older. In a small pilot study of long-acting, weekly PEG-2a in children 2 – 8 years of age with chronic HCV, SVR was 43% (46% in genotype 1) (13). In an open-label uncontrolled pilot study of the combination of PEG alfa-2b plus oral RV in children 2 – 17 years of age, Wirth et al (14) reported an SVR in genotype 1 patients of 48%. The combination of PEG alfa 2b with RV was recently approved for use in children in the US, based largely on results of this single, uncontrolled trial (14). Results of larger uncontrolled trials of combination therapy in children were recently published (15) (16) (17).

A major purpose of the present proposal was to perform a prospective trial with placebo control for RV to investigate whether or not the addition of RV to PEG-2a is truly necessary to achieve the highest efficacy in young subjects. A major potential problem in the treatment of subjects with chronic hepatitis C under the age of 18 years of age is that RV has been shown to be both teratogenic (18)(19) and embryotoxic in animals (20). The Ribavirin Pregnancy Registry is an ongoing attempt to assess the effects of (accidental) ribavirin exposure pregnancy in humans (21) which should clarify the consequences of maternal ribavirin intake on the human fetus.. Caution should be used when treating women of childbearing age with this drug. The need for a placebo-controlled trial was further supported by the data, detailed above, that children appear to respond better to interferon-based therapies than adults and that PEG alone in young children resulted in almost identical SVR rates in children with genotype 1 compared to pediatric trials of the combination of interferon and RV and to the combination of PEG and RV. For all of these reasons, the Pediatric Study of Hepatitis C (PEDS-C) was conducted as an adequately powered, randomized controlled multi-center trial of the safety and efficacy of PEG 2a with and without RV in children and adolescents with chronic hepatitis C.

Methods

Subjects

Subjects were enrolled by the investigators at each site from December 2004 until May 2006 at 11 U.S. medical centers (www.ClinicalTrials.gov). The study was completed as per the original design, with two years of off-therapy follow up. The last patient completed the two year follow up February 2010. Inclusion criteria included age 5 to 18 years with chronic HCV infection documented by the presence of HCV RNA in plasma on two occasions at least 6 months apart and chronic liver disease as indicated by inflammation and/or fibrosis consistent with chronic HCV infection on a liver biopsy obtained within the past 36 months as assessed by a qualified pathologist not consistent with other known liver diseases and not normal.. Other details are available at the Clinical Trials website and in our paper on the design of this trial (22).

Study design

The primary objective of the study was to determine if it is necessary to add RV to PEG 2a to maximize outcome of therapy of children with chronic hepatitis C. Figure 1 shows the flow of subjects through the study as well as the results of therapy. After informed consent, subjects were randomly assigned 1:1 to receive either PEG 2a and RV or PEG 2a and placebo. PEG 2a (Pegasys: Roche Pharmaceuticals, Nutley, NJ) was administered in a dose of 180 μg/1.73m^2 body surface area (maximum 180 μg) subcutaneously once weekly. The 180 μg/mL vial was used. Ribavirin (Copegus; Roche Pharmaceuticals) was administered in a dose of 15 mg/kg orally twice daily (maximum 1200 mg/day if ≥ 75 kg and 1000 mg if < 75 kg), using 100 mg tablets. Placebo tablets were supplied in the same dosing regimen as RV, using the same number of tablets that would be given if RV were being administered (e.g., 3 placebo tablets twice daily for a 40 kg child who would receive 3 100 mg RV tablets twice daily). Participants, families and investigators were blinded to ribavirin/placebo. Patients without detectable HCV RNA at 24 weeks were continued on treatment for another 24 weeks; whereas those who had detectable HCV RNA at 24 weeks were considered treatment failures. Patients who failed treatment with PEG 2a plus placebo were offered “open-label” therapy with PEG 2a plus RV for another 48 weeks (stopping after 24 weeks of “open-label” therapy if HCV RNA remained positive). The study protocol was conducted under an Investigational New Drug application held by the principal investigator and was approved by the institutional review boards of the participating sites. All parent/guardians

provided written informed consent and children over 12 years provided written assent prior to enrollment.

Randomization allocation sequences were generated at the data coordinating center which determined assignment of participants to therapeutic groups. Randomization was stratified by center according to HCV genotype (genotype 1 versus non- genotype 1). Allocations of each participant to a therapy group were conveyed to the centers via a centralized telephone service. Both the participants and the investigators were blinded as to the therapy group.

At baseline and weeks 24, 48, and 72, qualitative HCV RNA was assessed with Roche Cobas Amplicor HCV Qualitative PCR, v2.0 with a lower limit of detection of 60 IU/mL. In addition, quantitative HCV RNA assays were done at the conclusion of the study on plasma stored at −80 °C and thawed once. HCV RNA levels were measured at entry and weeks 1, 3, 5, 12, 24, 48, and 72 using a high-throughput quantitative assay (Cobas® TaqMan® HCV Test, v2.0.with High Pure System (Research Use Only) for Viral Nucleic Acid extraction, (Roche Molecular Systems, Pleasanton, CA) which has a lower limit of quantification of 25 IU/mL and a lower limit of detection of 10 IU/mL in EDTA plasma. HCV viral genotyping was performed at entry using a line-probe assay (LiPA, Innogenetics; Ghent, Belgium). Results are reported as genotype 1 or genotype non-1 (2, 3 or 6).

Assessments of health-related quality of life, body composition and growth, autoantibodies, and ophthalmologic status were performed (22) and results will be reported separately. The report on ophthalmologic status has been published (23). Baseline hepatic histology (24) and health-related quality of life results have been reported (25).

PEDS-C was funded in part by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) in collaboration with the Food and Drug Administration (FDA) Office of Orphan Products Development and under a contract between Johns Hopkins and Roche Laboratories, Inc. (Nutley, NJ). Roche supplied drugs and the costs of the data coordinating center and the central laboratory. Roche Molecular Systems (Alameda, CA) supported the quantitative viral testing. An external data and safety monitoring board (DSMB) appointed by NIDDK reviewed and approved the study design and monitored its conduct. Roche had no role in study design, oversight, analysis or interpretation and they were not represented on the DSMB. Investigators interpreted study results and prepared manuscripts independently.

Assessment of efficacy and safety

The primary outcome was the proportion of subjects with an SVR, defined as non-detectable HCV RNA in plasma (<10 IU/mL) at least 24 weeks after stopping treatment. Response rates were analyzed on an intent-to-treat basis. The secondary outcome measure was safety, assessed by vital signs, laboratory tests, and adverse events. The Pediatric AIDS toxicity table (26) was used as a guide for grading severity of adverse events. Medication compliance was assessed by coordinators' review of a medication diary completed by parent/guardians. Pill and vial counts were done by research coordinators and/or investigational pharmacists.

Virologic response rates during the study were defined using modifications of standard criteria (27). Rapid virologic response (RVR) was defined as lack of detectable HCV RNA in plasma at week 5. Early virologic response (EVR) was defined as ≥ 2 $\log_{10}$ IU/mL drop at week 12 compared to baseline. Patients who had no detectable HCV RNA in plasma at the end of therapy were considered to have an end-of-treatment virologic response. Those with an end-of-treatment response who became HCV RNA positive after stopping therapy were considered to have virologic relapse. Study medication dose adjustments were

standardized for laboratory toxicities (see Supplementary Table 1). If an adverse event continued despite maximal dose reduction, medication was discontinued.

Statistical analysis

PEDS-C was designed to have a statistical power of 80% (standard chi-square test of equality with 2-sided alpha=0.05) to detect an absolute difference of at least 25% in the proportion of SVR in the two treatment groups. All subjects randomized (n=114) were included in the primary efficacy analysis. Two subjects were lost to follow-up and despite response at 24 weeks were considered treatment failures (intent to treat basis.) All other dropouts were non-responders at 24 weeks.

A multivariate logistic model was constructed to predict SVR using baseline and results of HCV RNA quantification at 12 weeks. Significance was assessed using a Wald chi-square comparing the maximum likelihood estimate for each parameter against zero. For ease of presenting odds ratios, continuous variables were dichotomized at their mean. SAS statistical software (Version 9.1.3, SAS Institute, Cary, NC) was used for all analyses.

Results

Subject characteristics

Figure 1 shows the number of children randomized, treated, and followed. Baseline characteristics were similar in the two treatment groups (Table 1). Most children had early stage disease, only 5 (4%) had bridging fibrosis and 2 (2%) cirrhosis (24).

Treatment responses

The primary endpoint, an SVR, was met by 29 (53%, 95% CI: 40%, 66%) children in the PEG 2a plus RV group compared to only 12 (21%, 95% CI: 10%, 32%) of the PEG 2a plus placebo group ($p<0.001$). HCV RNA levels decreased in both treatment groups, but the average rate and degree of decline was greater among subjects receiving PEG 2a plus RV compared to PEG 2a plus placebo (Figure 2). Differences in HCV RNA decline became statistically significant by week 3 and remained significant to week 24.

HCV RNA was no longer detectable in a higher proportion of subjects treated with PEG 2a plus RV than with PEG 2a plus placebo at each time point from week 5 to week 48 of therapy as well as 24 weeks after stopping treatment (Figure 3). The higher SVR rate in the group treated with PEG 2a plus RV was related both to a higher end-of-treatment response (65% vs 37%: $p=0.002$) as well as a lower relapse rate after stopping therapy (17% vs 45%: $p=0.02$). Furthermore, the higher response rates with PEG 2a plus RV treatment occurred in both genotype 1 (47% vs 17%) as well as genotypes 2–4 infected patients (80% vs 36%). The higher response rate with PEG 2a plus RV vs PEG plus placebo therapy was present regardless of age, ALT level, or severity of liver histology (Table 2). The one exception to the increased SVR observed with PEG plus RV vs PEG plus placebo therapy was in the group with low HCV viral load, for whom both therapies resulted in high SVR rates (Table 2.)

In post-hoc, multivariate analysis, significant predictors of SVR were: therapy with PEG 2a plus RV (odds ratio [OR]=4.5, $p=0.013$), female gender (OR=4.5, $p=0.03$), non-maternal route of transmission of HCV (OR=6.9, $p=0.02$), genotype non-1 (OR=6.1, $p=0.02$), moderate or marked inflammation on liver histology (OR=4.2, $p=0.04$, absence of steatosis by liver histology (OR=3.9, $p=0.04$), and lower baseline HCV RNA levels (OR=5.5, $p=0.0008$). As shown in Figure 1, 33 subjects treated with PEG 2a plus placebo who were HCV RNA positive after 24 weeks were considered non-responders and were eligible for

"open-label" therapy with PEG 2a plus RV. Of these 33 children, 28 began the open-label therapy; 13 (46%), became HCV RNA negative after 24 weeks, and continued on therapy for another 24 weeks. Eleven of the 13 children (41% of the total) achieved a SVR. Thus, among the 57 children initially randomized to the PEG and placebo arm, 23 (40%) ultimately achieved an SVR, approximately half, however, having failed to clear HCV RNA on PEG monotherapy and requiring retreatment using both PEG and RV.

Patterns of virologic response during the first 12 weeks as predictors of SVR according to genotype

While only a small number of children had an RVR (9% of genotype 1 patients, 100% of those children with RVR experienced an SVR (Table 3). Previous studies in adults have shown that the lack of an EVR is highly predictive of non-response and can be used as a means of stopping therapy early in patients in whom therapy is likely to be futile (28). In this study, 91 children or adolescents with genotype 1 infection were treated, among whom an EVR was achieved in 71% (32/45) of those treated with PEG plus RV versus only 40% (18/46) of recipients of PEG plus placebo. Among the 41 subjects with genotype 1 who did not achieve an EVR, 3 (7%) nevertheless had a SVR including 1 on therapy with PEG plus RV and 2 receiving PEG plus placebo.

Durability of response at years one and two of follow-up

As shown in Figure 1, 47 (87%) of the 55 children originally randomized to PEG plus RV were followed up at Year 1 and 45 (82%) at Year 2. Of the 59 children originally randomized to PEG plus placebo, comparable numbers were 51 (86%) for both years. For those children achieving an SVR 72 weeks after initiation of therapy who were followed for two years, durability of viral response was 100%.

Safety, adverse events and adherence

Influenza-like, headache, and gastrointestinal symptoms occurred in almost all children and the frequency of all AE's did not differ between treatment groups with the exception of the influenza-like AE's which were actually less frequent in the "open-label" group (Supplementary Table2). Therapy led to significant declines in total white blood cell counts, absolute neutrophil counts and hemoglobin which returned to baseline when therapy was stopped (Figure 4A/B). Declines in white blood cell and neutrophil counts and hemoglobin were greater in patients treated with PEG2a plus RV than in recipients of PEG2a plus placebo. Overall, 27% of subjects required dose reduction for neutropenia as early as the first week of therapy. Neutropenia was not associated with increased rates of bacterial infections. Dose reductions of PEG2a or RV were common (Supplementary Table 3) but appeared to have little effect on SVR rates in either group. In subjects treated with PEG2a plus RV, the SVR was 44% in those with no dose reductions of PEG2a versus 61% for those with one or more reductions ($p=0.23$). In subjects treated with PEG 2a plus placebo, the SVR rate was 27% in those with no dose reduction of PEG2a versus 16% for those with dose reductions ($p=0.32$). Adherence was excellent overall with rates of 95% or higher for adherence to 90% of the prescribed doses of PEG/RV or PEG/placebo (Supplementary Table 3.)

Therapy was discontinued early in 5 of 114 (4%) subjects, four treated with PEG 2a plus RV (one each for transient blindness, retinal exudates, suicide gesture, and new onset juvenile diabetes mellitus) compared to one patient-treated with PEG 2a plus placebo (withdrawn for aggressive behavior). These side effects were reported as possibily secondary to the drug therapy The suicide gesture and diabetes both led to hospitalization and were thus considered serious adverse events as was the one liver biopsy complication, which required hospitalization The child with the liver biopsy complication had undergone percutaneous

liver biopsy by a physician who referred the child to the study and the child was enrolled soon thereafter. The liver biopsy resulted in an initially occult perforation of the gallbladder, not evident at the time of enrollment, which eventually resulted in hospitalization and cholecystectomy. Given that the hospitalization occurred after enrollment the hospitalization was technically considered a serious adverse event. Two children developed hypothyroidism by week 24 of therapy. One resolved off therapy. One did not and was treated with thyroxine.

Discussion

This prospective, randomized controlled trial has demonstrated that the addition of RV to PEG alfa-2a significantly increases early as well as sustained response rates. Therapy with PEG 2a plus RV was superior to PEG 2a plus placebo regardless of age, ALT levels, and degree of histologic severity. The single exception to the superiority of combination therapy was in the small group of children with HCV RNA levels <600,000 IU/mL who responded well regardless of whether RV was used. These results indicate that children with chronic hepatitis C should not receive PEG monotherapy. The response rates in this trial were comparable to those in uncontrolled clinical trials of PEG and RV in children (14) and were similar to rates reported in adults (27)(28)(29)(30)(31)(32). The mechanism by which RV increases response rates in hepatitis C is unclear, but may include effects on viral replication, error-prone mutagenesis, decreased intracellular IMPDH, and enhanced immune response (334).

Changes in HCV RNA levels early in the course of therapy have been reported to be useful in predicting ultimate sustained responses. In this study, SVR was achieved by all children treated with combination therapy who had RVR at week 5 and 65% of those with an EVR at week 12. Importantly, however, 3 children who did not achieve an EVR, nevertheless had a sustained response, so that the negative predictive value of EVR was not reliable enough to be used to stop therapy. These findings indicate that children should be given the benefit of 24 weeks of therapy before stopping therapy because of futility of continuing treatment.

In multivariate analysis, the most important associations with sustained response were combination therapy vs PEG alone (p=0.001) and lower vs higher baseline HCV levels. After adjustment for other factors, children with lower baseline HCV levels showed a higher probability of SVR((p=0.0008). As in other studies, subjects with HCV genotype 1 had lower SVR rates compared to those with the other genotypes (29).

Safety and drug dosage

In PEDS-C, the addition of RV to PEG 2a therapy increased response rates markedly, with little change in side effect profile. Decrease in hematocrit and neutrophils was greater in the children receiving both PEG and RV compared to those receiving PEG and placebo, but rates of dose modification and discontinuations and serious adverse events were similar. Since neutropenia occurred in one-third of subjects, children treated with this drug combination needed careful monitoring. Rates of depression were lower in children than in adults (34).

Costs of HCV infection

Chronic HCV infection is costly. Jhaveri et al (2) projected that during the next decade, $26 million will be spent for screening, $117–206 million for monitoring, and $56 – 104 million for treating children with HCV. While there have been only rare instances of hepatocellular carcinoma(7) and end-stage liver disease requiring liver transplantation as a result of HCV infection in childhood (6), the proportion progressing to these end-points will undoubtedly

rise in adulthood in these patients infected early in life. The precise indications for treating the child with chronic HCV are evolving and are probably different than for adults, given that predictors of liver disease progression have not been elaborated for the child with chronic HCV. Eradication of the virus in an infected child has the dual benefits of eliminating social stigma as well as the progression of liver disease. As noted in the recent AASLD Practice Guidelines on the Treatment of HCV, some would argue against routine treatment for children on the basis of the generally mild liver disease (27). However others propose that treatment of children is equally reasonable given that the average child is likely to be infected for five decades or more. Chronic hepatitis C is also a costly disease in terms of medical and psychological consequences and social stigma (35). Thus, the identification of safe and effective treatments for children suffering from HCV infection should proceed as rapidly as possible.

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The statistical analysis of the entire data sets pertaining to efficacy (specifically primary and major secondary efficacy endpoints) and safety (specifically, serious adverse events as defined in federal guidelines) have been independently confirmed by a biostatistician who is not employed by the corporate entity; and 2) the corresponding author had full access to all of the data and takes full responsibility for the veracity of the data and analysis. Roche Pharmaceuticals had no role in the study design nor in the collection, analysis, and interpretation of data.

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Abbreviations

EVR	(early virologic response)
HCV	hepatitis C virus
PEG	(peginterferon)
RVR	(rapid virologic response)
RV	(ribavirin)
SVR	(sustained viral response)

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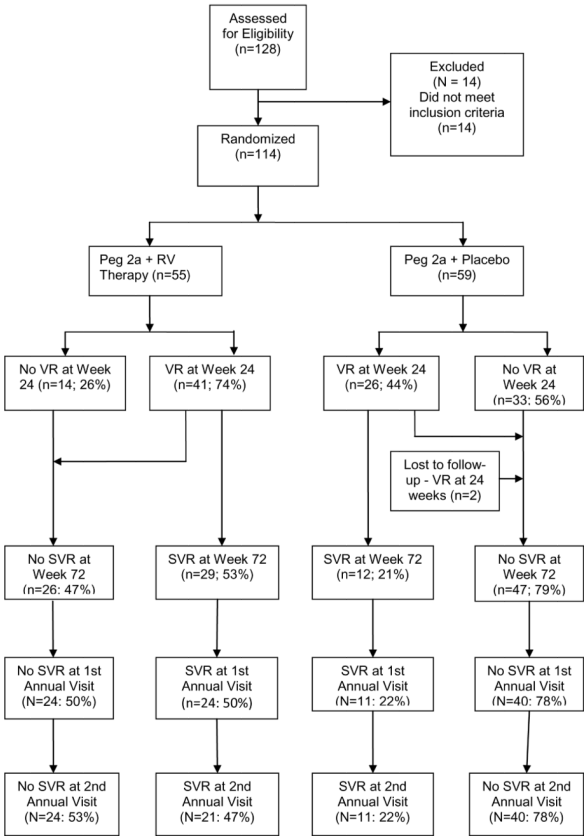

Figure 1.
CONSORT Diagram
Differences in n between Week 72 and n at the second annual visit = patients lost to follow up (total of 10 for PEG 2a plus RV and 8 for PEG 2a plus placebo.)

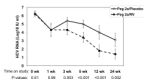

Figure 2.
Mean Log_{10} HCV RNA levels during the first 24 weeks of treatment by time on study (weeks) and treatment group

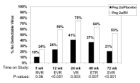

Figure 3.
Percent of patients with no detectable virus by time on study (weeks) and treatment group

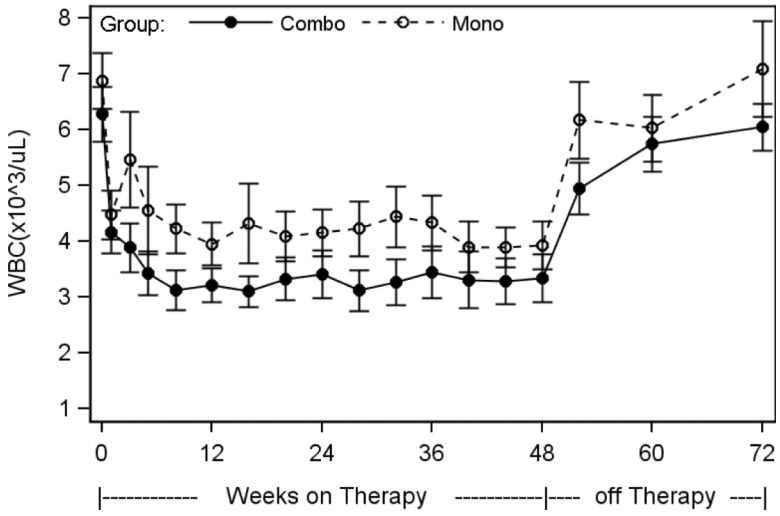

Figure 4A.
White Blood Cells (WBC × $10^3/\mu L$) by Time on Study (Weeks) and Treatment Group

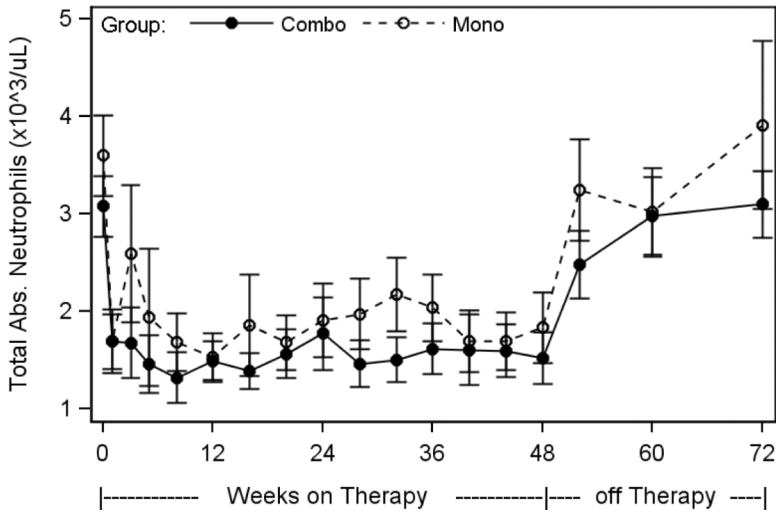

Figure 4B.
Absolute Neutrophil Count (ANC × 10^3/μL) by Time on Study (Weeks) and Treatment Group

Table 1

Baseline Characteristics according to Treatment Group

	Peginterferon + Ribavirin (n=55)	Peginterferon + Placebo (n=59)
Patient Characteristics		
Age (Years)	10.7 (±3.3)	10.8 (±3.6)
5–11	30 (54%)	30 (51%)
12–18	25 (46%)	29 (49%)
Sex – Female	28 (51%)	23 (39%)
Race – Non-Caucasian	12 (22%)	17 (29%)
BMI Z-scores	0.8 (±1.0)	0.7 (±1.1)
Total CDI raw score	5.9 (±4.2)	5.9 (±4.6)
Mode of acquisition		
Maternal-infant	39 (71%)	47 (80%)
Transfusion	6 (11%)	2 (3%)
Other	10 (19%)	10 (18%)
Est. duration of infection (mo.)	105 (±56)	111 (±55)
Genotype		
1	45 (82%)	47 (80%)
2	4 (7%)	3 (5%)
3	6 (11%)	7 (12%)
6	0 (0%)	2 (3%)
Baseline Laboratory Measures		
ALT (U/L)	49 (±59)	49 (±59)
ALT > Upper Limit of Normal	32 (58%)	38 (64%)
AST (U/L)	45 (±40)	45 (±29)
AST > Upper Limit of Normal	28 (51%)	28 (47%)
Baseline HCV RNA Levels		
HCV RNA $\log_{10}$ IU/mL	6.2 (±0.8)	6.3 (±0.9)
HCV RNA ≥ 600,000 IU/mL	32 (70%)	46 (82%)
Histology Results		
Histology Activity Index*		
Minimal (1–3)	23 (43%)	24 (43%)
Mild (4–6)	10 (19%)	10 (18%)
Moderate (7–9)	19 (35%)	21 (38%)
Marked (10–12)	2 (4%)	1 (2%)
Steatosis*		
None	29 (54%)	34 (61%)
Minimal (≤ 5% of tissue)	21 (39%)	17 (30%)
Mild (6%–33%)	4 (7%)	5 (9%)

	Peginterferon + Ribavirin (n=55)	**Peginterferon + Placebo (n=59)**
Fibrosis Score*		
None	7 (13%)	8 (14%)
Portal-Periportal fibrosis (Ishak 1–2)	43 (80%)	46 (82%)
Bridging Fibrosis (Ishak 3–4)	4 (7%)	1 (2%)
Cirrhosis (Ishak 5–6)	0 (0%)	1 (2%)

Note: Results presented as n (%) or mean ± s.d. Results for ALT, AST and HCV RNA presented as geometric mean ± s.d. No comparison shows a significant difference ($p<0.05$) between Peg interferon + Ribavirin and Peginterferon + Placebo groups. CDI=Childhood Depression Index

*Sample size for pathology variables: Peg interferon + Ribavirin therapy n=54, Peginterferon + Placebo n=56

Table 2

Virologic Results by Treatment Group and Baseline Features

	(Sustained Virologic Response percent) [95% Confidence Interval]		
	Peginterferon/ribavirin (N=55)	**Peginterferon/placebo (N=57)**	**P-Value**
Total	29/55 (53%) [40%, 66%]	12/57 (21%) [10%, 32%]	.0005
Genotype 1	21/45 (47%) [32%, 61%]	8/46 (17%) [6%, 28%]	.0027
2 – 6	8/10 (80%) [55%, 100%]	4/11 (36%) [8%, 65%]	.0563*
Female	15/28 (54%) [35%, 72%]	8/23 (35%) [15%, 54%]	.1797
Male	14/27 (52%) [33%, 71%]	4/34 (12%) [1%, 23%]	.0007
Age <=11 years	15/30 (50%) [32%, 68%]	7/29 (24%) [9%, 40%]	.0400
>=12 years	14/25 (56%) [37%, 75%]	5/28 (18%) [4%, 32%]	.0038
White	22/43 (51%) [36%, 66%]	8/40 (20%) [8%, 32%]	.00031
Non-White	7/12 (58%) [30%, 86%]	4/17 (24%) [3%, 44%]	.0651*
ALT Normal	16/23 (70%) [51%, 88%]	6/20 (30%) [10%, 50%]	0.0096
> ULN	13/32 (41%) [24%, 58%]	6/37 (16%) [4%, 28%]	0.0246
HCV RNA < 600,000 IU/ml	16/23 (70%)	10/13 (78%)	*p = 0.73*
HCV RNA ≥ 600,000 IU/ml	16/32 (50%)	5/46 (11%)	p = 0.0002
Inflammation (Histology Activity Index)			
Minimal (1–3)	10/23 (43%) [23%, 64%]	5/24 (21%) [5%, 37%]	0.0959
Mild-Marked (4–12)	18/31 (58%) [41%, 75%]	6/30 (20%) [6%, 34%]	0.0023
Fibrosis (Ishak stage)			
None	3/7 (43%) [6%, 80%]	3/8 (38%) [4%, 71%]	0.8327
Stage 1–6	25/47 (53%) [39%, 67%]	8/48 (17%) [6%, 27%]	0.0003
Steatosis			
Present	9/25 (36%) [17%, 55%]	1/21 (5%) [0%, 14%]	0.0105
Absent	19/29 (66%) [48%, 83%]	10/33 (30%) [15%, 46%]	0.0056

Table 3a

Patterns of Viral Response as Predictors of Sustained Viral Response in Children with Genotype 1 treated with PegiInterferon plus Ribavirin

Response	% Achieving Response	% with Response Achieving SVR	PPV	NPV
1 log drop - Week 1	61%	50%	0.50	0.43
RVR (no detectable virus) - Week 5	15%	100%	1.00	0.64
EVR (2 log drop) - Week 12	71%	65%	0.65	0.78

Table 3b

Patterns of Viral Response as Predictors of Sustained Viral Response in Children with Genotype 1 treated with Peginterferon plus Placebo

Response	% Achieving Response	% With Response Achieving SVR	PPV	NPV
1 log drop - Week 1	66%	21%	0.21	0.85
RVR (no detectable virus) - Week 5	4%	100%	1.00	0.85
EVR (2 log drop) - Week 12	40%	43%	0.43	0.95

Table 3c

Patterns of Viral Response as Predictors of Sustained Viral Response in Children with Genotype 1 treated with Peginterferon plus Ribavirin or Peginterferon plus Placebo

Response	% Achieving Response	% With Response Achieving SVR	PPV	NPV
1 log drop - Week 1	64%	37%	0.37	0.63
RVR (no detectable virus) - Week 5	9%	100%	1.00	0.75
EVR (2 log drop) - Week 12	55%	56%	0.56	0.89

Notes: PPV = probability of SVR given earlier response NPV = probability of no SVR given no earlier response