CLINICAL ADVANCES IN LIVER, PANCREAS, AND BILIARY TRACT

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

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BACKGROUND & AIMS: Although randomized trials of adults infected with hepatitis C virus (HCV) have shown that ribavirin increases the 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 to 17 years old with chronic hepatitis C. **METHODS:** HCV RNA–positive children from 11 university medical centers were randomly assigned to receive either PEG alfa-2a (PEG-2a; 180 μg/1.73 m^2 body surface area, subcutaneously each week; n = 55) and ribavirin (15 mg/kg orally in 2 doses daily) or PEG-2a and placebo (n = 59) for 48 weeks. The primary end point was sustained virologic response (SVR; lack of detectable HCV RNA at least 24 weeks after stopping therapy). **RESULTS:** SVR was achieved in 53% of children treated with PEG-2a and ribavirin, compared with 21% of children who received PEG-2a and placebo ($P < .001$). Early virologic response (HCV RNA reduction >2 $\log_{10}$ IU 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; Multicenter Pediatric Trial.

Recently published data regarding the prevalence of chronic hepatitis C virus (HCV) infection in children in the United States 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 that 23,048 to 42,296 children are chronically infected with HCV and 7200 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]

Abbreviations used in this paper: CI, confidence interval; EVR, early virologic response; OR, odds ratio; PEDS-C, Pediatric Study of Hepatitis C; PEG, pegylated interferon; PEG-2a, pegylated interferon alfa-2a; RV, ribavirin; RVR, rapid virologic response; SVR, sustained viral response.

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Although chronic hepatitis C appears to run a more benign course in children compared with adults,[4] significant histologic 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 interferon alfa alone to the combination of interferon with ribavirin (RV) and, most recently, to the combination of pegylated interferon (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% to 50% among patients with genotype 1 (representing 60%–70% of US patients) to 70% to 80% among patients with genotypes 2 or 3 (20%–30% of patients).[8]

Recommendations for treatment of 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% to 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 dose of interferon in children (3 MU/m^2)[11,12] as opposed to that used in treating adults (3 MU/1.73 m^2), the generally lower viral load in children, relatively mild liver disease, and/or other factors.

This combination therapy, which resulted in a sustained virologic response (SVR) of 46% (54/118 children) in a large multicenter pediatric study,[11] is now approved by the Food and Drug Administration for children 3 years of age and older. In a small pilot study of long-acting, weekly PEG alfa-2a (PEG-2a) in children 2 to 8 years of age with chronic HCV infection, 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 to 17 years of age, Wirth et al[14] reported an SVR in patients with genotype 1 of 48%. The combination of PEG alfa-2b with RV was recently approved for use in children in the United States, based largely on the results of this single uncontrolled trial.[14] Results of larger uncontrolled trials of combination therapy in children were recently reported.[15–17]

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 who are younger than 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) RV exposure pregnancy in humans,[21] which should clarify the consequences of maternal RV 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 previously, 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 with pediatric trials of the combination of interferon and RV and compared with 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, multicenter trial of the safety and efficacy of PEG-2a with and without RV in children and adolescents with chronic hepatitis C.

Subjects and Methods

Subjects

Subjects were enrolled by the investigators at each site from December 2004 to May 2006 at 11 US medical centers (www.ClinicalTrials.gov). The study was completed as per the original design, with 2 years of off-therapy follow-up. The last patient completed the 2-year follow-up in February 2010. Inclusion criteria included age 5 to 18 years with chronic HCV infection documented by the presence of HCV RNA in plasma on 2 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 specimen 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 ClinicalTrials.gov Web site and in our report 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. Supplementary 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/1.73 m^2 body surface area (maximum 180 μg) subcutaneously once weekly. The 180-μg/mL vial was used. RV (Copegus; Roche Pharmaceuticals) was administered in a dose of 15 mg/kg orally twice daily (maximum 1200 mg/day if $\geq$75 kg and

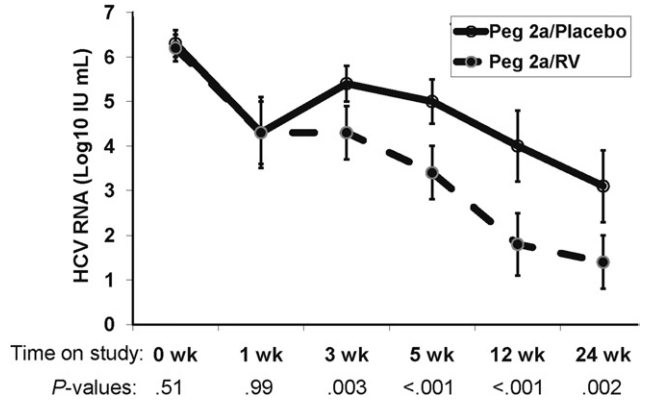


Figure 1. Mean $\log_{10}$ HCV RNA levels during the first 24 weeks of treatment by time on study (weeks) and treatment group.

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 (eg, 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 RV/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 to respond to 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 older than 12 years provided written assent before 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 vs nongenotype 1). Allocation of each participant to a therapy group was 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 Cobas Amplicor HCV v2.0 (Roche) qualitative polymerase chain reaction with a lower limit of detection of 60 IU/mL. In addition, quantitative HCV RNA assays were performed 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 (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 in collaboration with the Food and Drug Administration Office of Orphan Products Development and under a contract between Johns Hopkins and Hoffman LaRoche (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 appointed by the National Institute of Diabetes and Digestive and Kidney Diseases reviewed and approved the study design and monitored its conduct. Roche had no role in study design, oversight, analysis, or interpretation and was not represented on the data and safety monitoring board. 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 nondetectable 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 performed 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 a decrease ≥2 $\log_{10}$ IU/mL at week 12 compared with 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. Dose adjustments of study medication 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 χ^2 test of equality with 2-sided $\alpha = .05$) to detect an absolute difference of at least 25% in the proportion of SVR in the 2 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 nonresponders 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 χ^2 comparing the maximum likelihood estimate for each parameter against zero. For ease of presenting odds ratios (ORs), continuous variables were dichotomized at their mean. SAS statistical software (version 9.1.3; SAS Institute Inc, Cary, NC) was used for all analyses.

Results

Subject Characteristics

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

Treatment Responses

The primary end point, an SVR, was met by 29 children (53%; 95% confidence interval [CI], 40%–66%) in the PEG-2a plus RV group compared with only 12 (21%; 95% CI, 10%–32%) in the PEG-2a plus placebo group ($P < .001$). 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 with PEG-2a plus placebo (Figure 1). Differences in HCV RNA decline became statistically significant by week 3 and remained significant to week 24.

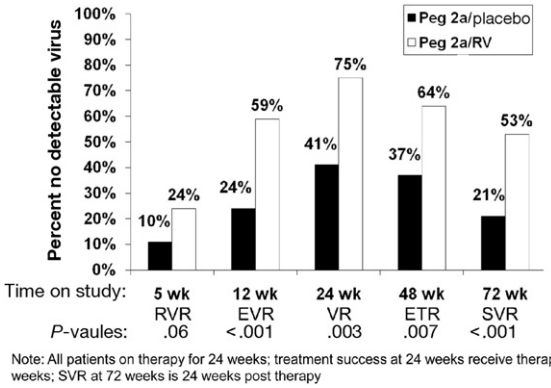
HCV RNA was no longer detectable in a higher proportion of subjects treated with PEG-2a plus RV than with PEG-2a plus placebo at each time point from week 5 to week 48 of therapy as well as 24 weeks after stopping treatment (Figure 2). The higher SVR rate in the group treated with PEG-2a plus RV was related both to a higher end-of-treatment response (65% vs 37%; $P = .002$) and a lower relapse rate after stopping therapy (17% vs 45%; $P = .02$). Furthermore, the higher response rates with PEG-2a plus RV treatment occurred in both patients with genotype 1 (47% vs 17%) as well as patients with genotypes 2–4 (80% vs 36%). The higher response rate with PEG-2a plus RV versus PEG plus placebo therapy was present regardless of age, alanine aminotransferase level, or severity of liver histology (Table 2). The one exception to the increased SVR observed with PEG plus RV versus PEG plus placebo therapy was in the group with low HCV viral load, for whom both therapies resulted in high SVR rates (Table 2).

Table 1. Baseline Characteristics According to Treatment Group

	PEG + RV (n = 55)	PEG + placebo (n = 59)
Patient characteristics		
Age (*y*)	10.7 (±3.3)	10.8 (±3.6)
5–11	30 (54%)	30 (51%)
12–17	25 (46%)	29 (49%)
Sex (female)	28 (51%)	23 (39%)
Race (nonwhite)	12 (22%)	17 (29%)
Body mass index Z-scores	0.8 (±1.0)	0.7 (±1.1)
Total Childhood Depression Index 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%)
Estimated 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		
Alanine aminotransferase (*U/L*)	49 (±59)	49 (±59)
Alanine aminotransferase level greater than the upper limit of normal	32 (58%)	38 (64%)
Aspartate aminotransferase (*U/L*)	45 (±40)	45 (±29)
Aspartate aminotransferase level greater than the 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[a]		
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[a]		
None	29 (54%)	34 (61%)
Minimal (≤5% of tissue)	21 (39%)	17 (30%)
Mild (6%–33%)	4 (7%)	5 (9%)
Fibrosis score[a]		
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 are presented as n (%) or mean ± SD. Results for alanine aminotransferase, aspartate aminotransferase, and HCV RNA are presented as geometric mean ± SD. No comparison shows a significant difference ($P < .05$) between the PEG plus RV and PEG plus placebo groups.

[a]Sample size for pathology variables: PEG plus RV, n = 54; PEG plus placebo, n = 56.



Note: All patients on therapy for 24 weeks; treatment success at 24 weeks receive therapy through 48 weeks; SVR at 72 weeks is 24 weeks post therapy

Figure 2. Percent of patients with no detectable virus by time on study (weeks) and treatment group.

In post hoc multivariate analysis, significant predictors of SVR were therapy with PEG-2a plus RV (OR, 4.5; $P = .013$), female sex (OR, 4.5; $P = .03$), nonmaternal route of transmission of HCV (OR, 6.9; $P = .02$), genotype non-1 (OR ,6.1; $P = .02$), moderate or marked inflammation on liver histology (OR, 4.2; $P = .04$), absence of steatosis by liver histology (OR, 3.9; $P = .04$), and lower baseline HCV RNA levels (OR, 5.5; $P = .0008$). As shown in Supplementary Figure 1, 33 subjects treated with PEG-2a plus placebo who were HCV RNA positive after 24 weeks were considered nonresponders 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 an SVR. Thus, among the 57 children initially randomized to the PEG and placebo arm, 23 (40%) ultimately achieved an SVR; approximately half, however, failed to clear HCV RNA on PEG monotherapy and required re-treatment with both PEG and RV.

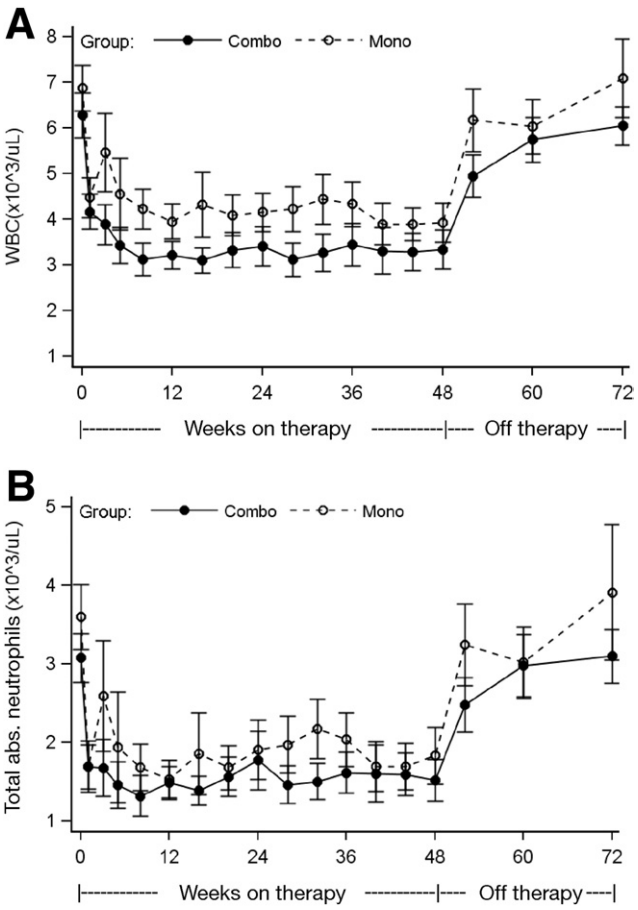


Figure 3. (*A*) Total white blood cell count and (*B*) absolute neutrophil count during therapy.

Table 2. Virologic Results by Treatment Group and Baseline Features

	PEG/RV (n = 55)	PEG/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
Genotype 2–6	8/10 (80%) [55%–100%]	4/11 (36%) [8%–65%]	.0563[a]
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 y or younger	15/30 (50%) [32%–68%]	7/29 (24%) [9%–40%]	.0400
Age 12 y or older	14/25 (56%) [37%–75%]	5/28 (18%) [4%–32%]	.0038
White	22/43 (51%) [36%–66%]	8/40 (20%) [8%–32%]	.00031
Nonwhite	7/12 (58%) [30%–86%]	4/17 (24%) [3%–44%]	.0651
Normal alanine aminotransferase level	16/23 (70%) [51%–88%]	6/20 (30%) [10%–50%]	.0096
Alanine aminotransferase level greater than the upper limit of normal	13/32 (41%) [24%–58%]	6/37 (16%) [4%–28%]	.0246
HCV RNA <600,000 IU/mL	16/23 (70%)	10/13 (78%)	.73
HCV RNA ≥600,000 IU/mL	16/32 (50%)	5/46 (11%)	.0002
Inflammation (Histology Activity Index)			
Minimal (1–3)	10/23 (43%) [23%–64%]	5/24 (21%) [5%–37%]	.0959
Mild-marked (4–12)	18/31 (58%) [41%–75%]	6/30 (20%) [6%–34%]	.0023
Fibrosis (Ishak stage)			
None	3/7 (43%) [6%–80%]	3/8 (38%) [4%–71%]	.8327
Stage 1–6	25/47 (53%) [39%–67%]	8/48 (17%) [6%–27%]	.0003
Steatosis			
Present	9/25 (36%) [17%–55%]	1/21 (5%) [0%–14%]	.0105
Absent	19/29 (66%) [48%–83%]	10/33 (30%) [15%–46%]	.0056

NOTE. Values in parentheses represent the percentage of SVR, and values in brackets represent 95% CIs.

Table 3. Patterns of Viral Response as Predictors of SVR in Children With Genotype 1

Response	Percent achieving response	Percent with response achieving SVR	Positive predictive value	Negative predictive value
PEG plus RV				
1-log decrease at week 1	61	50	0.50	0.43
RVR (no detectable virus) at week 5	15	100	1.00	0.64
EVR (2-log decrease) at week 12	71	65	0.65	0.78
PEG plus placebo				
1-log decrease at week 1	66	21	0.21	0.85
RVR (no detectable virus) at week 5	4	100	1.00	0.85
EVR (2-log decrease) at week 12	40	43	0.43	0.95
PEG plus RV or PEG plus placebo				
1-log decrease at week 1	64	37	0.37	0.63
RVR (no detectable virus) at week 5	9	100	1.00	0.75
EVR (2-log decrease) at week 12	55	56	0.56	0.89

NOTE. Positive predictive value indicates probability of SVR given earlier response, and negative predictive value indicates probability of no SVR given no earlier response.

Patterns of Virologic Response During the First 12 Weeks as Predictors of SVR According to Genotype

Although only a small number of children had an RVR (9% of patients with genotype 1), 100% of those children with an RVR experienced an SVR (Table 3). Previous studies in adults have shown that the lack of an EVR is highly predictive of nonresponse 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 one on therapy with PEG plus RV and 2 receiving PEG plus placebo.

Durability of Response at Years 1 and 2 of Follow-up

As shown in Supplementary Figure 1, 48 (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 up for 2 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 adverse events did not differ between treatment groups with the exception of the influenza-like adverse events, which were actually less frequent in the open-label group (Supplementary Table 2). Therapy led to significant declines in total white blood cell counts, absolute neutrophil counts, and hemoglobin levels, which returned to baseline when therapy was stopped (Figure 3*A* and *B*). Declines in white blood cell and neutrophil counts and hemoglobin levels were greater in patients treated with PEG-2a plus RV than in recipients of PEG-2a 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 PEG-2a or RV were common (Supplementary Table 3) but appeared to have little effect on SVR rates in either group. In subjects treated with PEG-2a plus RV, the SVR was 44% in those with no dose reductions of PEG-2a versus 61% for those with one or more reductions (P = .23). In subjects treated with PEG-2a plus placebo, the SVR rate was 27% in those with no dose reduction of PEG-2a versus 16% for those with dose reductions (P = .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 subjects (4%), including 4 treated with PEG-2a plus RV (one each for transient blindness, retinal exudates, suicide gesture, and new-onset type 1 diabetes mellitus) and one patient treated with PEG-2a plus placebo (withdrawn for aggressive behavior). These side effects were reported as possibly 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 chil-

dren 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 shown 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, alanine aminotransferase 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.[27–32] 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 inosine 5′-monophosphate dehydrogenase, and enhanced immune response.[33,34]

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 an 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 the futility of continuing treatment.

In multivariate analysis, the most important associations with sustained response were combination therapy versus PEG alone ($P = .001$) and lower versus higher baseline HCV levels. After adjustment for other factors, children with lower baseline HCV levels showed a higher probability of SVR ($P = .0008$). As in other studies, subjects with HCV genotype 1 had lower SVR rates compared with 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 levels and neutrophil counts was greater in the children receiving both PEG and RV compared with those receiving PEG and placebo, but rates of dose modification and discontinuations and serious adverse events were similar. Because 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 to $206 million for monitoring, and $56 to $104 million for treating children with HCV. Although 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 American Association for the Study of Liver Diseases 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 5 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 with HCV infection should proceed as rapidly as possible.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at doi: 10.1053/j.gastro.2010.10.047.

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Conflicts of interest

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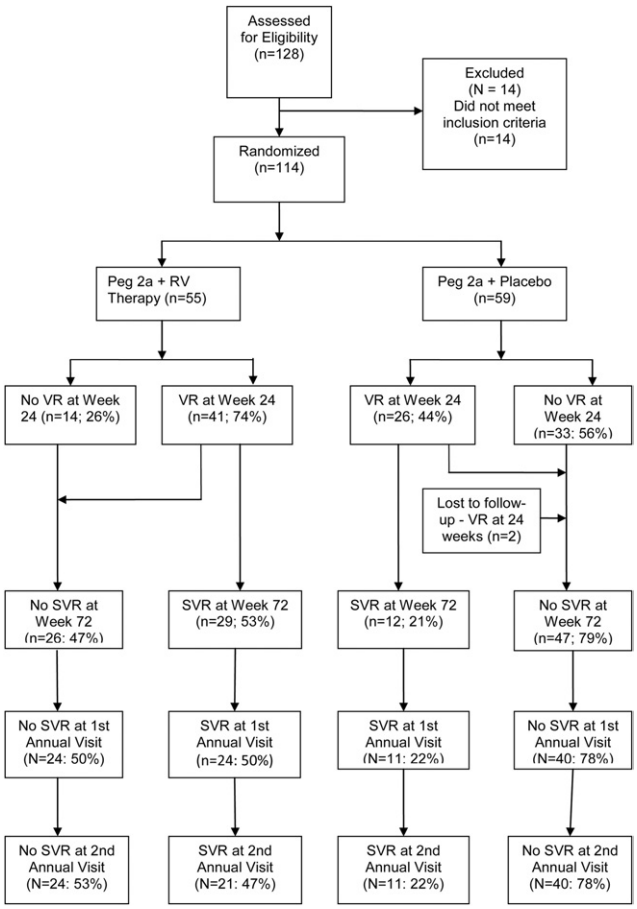

Supplementary Figure 1. CONSORT diagram. Differences in n between week 72 and n at the second annual visit equal patients lost to follow-up (total of 10 for PEG-2a plus RV and 8 for PEG-2a plus placebo).