Research Article

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High sustained virologic response rates in children with chronic hepatitis C receiving peginterferon alfa-2b plus ribavirin

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Background & Aims: Pegylated interferon (PEG-IFN) alfa-2b plus ribavirin (RBV) is the standard of care for adults with chronic hepatitis C but was not approved for the treatment of children at the time of this study. The aim of this study was to evaluate the efficacy and safety of PEG-IFN alfa-2b plus RBV in children.

Methods: Children and adolescents ages 3–17 years were treated with PEG-IFN alfa-2b (60 μg/m^2/week) plus RBV (15 mg/kg/day). The duration of therapy was 24 weeks for genotype (G) 2 and G3 patients with low viral load (<600,000 IU/ml) and 48 weeks for G1, G4, and G3 with high viral load (⩾600,000 IU/ml). The primary end point was sustained virologic response (SVR), defined as undetectable hepatitis C virus (HCV) RNA 24 weeks after completion of therapy.

Results: SVR was attained by 70 (65%) children. Genotype was the main predictor of response: G1, 53%; G2/3, 93%; G4, 80%. SVRs were similar in younger and older children. Baseline viral load was the main predictor of response in the G1 cohort. No new safety signals were identified, and adverse events (AEs) were generally mild or moderate in severity. Dose was modified because of AEs in 25% of children; 1 child discontinued because of an AE (thrombocytopenia). No serious AEs related to study drugs were reported.

Conclusion: Therapy with PEG-IFN alfa-2b plus RBV in children and adolescents with chronic hepatitis C offers favorable efficacy, reduced injection frequency, and an acceptable safety profile.

Introduction

Pegylated interferon (PEG-IFN) alfa in combination with ribavirin (RBV) is standard of care for adults with chronic hepatitis C (CHC). Recently, PEG-IFN alfa-2b in combination with RBV was approved in the US for children age 3 years and older [1]. The main advantage of PEG-IFN alfa is the extended serum half-life conferred by pegylation of the IFN molecule, which permits a once-weekly administration regimen with improved efficacy and a safety profile similar to that of IFN alfa [2,3]. To date, studies of PEG-IFN alfa in children and adolescents have been limited to a few pilot studies with small patient numbers and non-standardized treatment regimens [4–6].

Keywords: Pediatric; Hepatitis C virus genotype; Efficacy; Safety; Viral load.
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Abbreviations: PEG-IFN, pegylated interferon; RBV, ribavirin; CHC, chronic hepatitis C; HCV, hepatitis C virus; SVR, sustained virologic response; ALT, alanine aminotransferase; EVR, early virologic response; AE, adverse event.

Research Article

In the US, the seroprevalence of hepatitis C virus infection is 0.2% among children and 0.4% among adolescents [7], and comparable or slightly lower prevalence data have been reported in Western Europe, South America, and Taiwan [8–10]. Because viral transmission from blood transfusion has been virtually eliminated in the past two decades, vertical infection is now responsible for most new cases of HCV infection among children in the Western world. Although progression of liver disease in children with CHC is slow, severe fibrosis and cirrhosis may develop in approximately 5% of infected children by the time they reach adulthood [11]. Thus, pediatric hepatitis C is an important health care issue, with associated costs in the US estimated between $17 and $40 million annually [12]. Effective early treatment of hepatitis C in children can prevent the long-term consequences of chronic infection, improving patient prognosis and reducing health care expenditures.

Previous studies suggest that children treated with conventional IFN alfa or PEG-IFN alfa combined with RBV attain SVR rates similar to or better than those of adults [4,6]. Treatment should be considered for children with CHC because it provides high response rates with improved tolerability, alleviating the long-term sequelae and psychological burden of the disease.

The aim of this study was to evaluate the efficacy, tolerability, and pharmacokinetics of treatment with PEG-IFN alfa-2b plus RBV in children with CHC.

Patients and methods

Study design

This was a global, multicenter, open-label study to evaluate the efficacy, safety, and pharmacokinetics of PEG-IFN alfa-2b (PegIntron; Schering-Plough, Kenilworth, NJ) plus ribavirin (Rebetol; Schering-Plough) in pediatric patients with CHC (NCT00104052). The study was approved by the institutional review boards or ethics committees of the participating sites and conducted according to good clinical practice. Written informed consent was obtained from all parents or legal guardians, and patient assent was obtained, where appropriate.

Patients

Children ages 3–17 years with previously untreated CHC were enrolled. Prior to treatment, patients had an absolute neutrophil count $\geqslant 1500/mm^3$, platelet count $\geqslant 100{,}000/mm^3$, and hemoglobin levels $\geqslant 11$ g/dl for girls and $\geqslant 12$ g/dl for boys. Key exclusion criteria included decompensated liver disease, coexisting HIV or hepatitis B virus infection, hemoglobinopathy, hemophilia, malignant or immunologic diseases, preexisting neurologic or psychiatric disorder, retinopathy, substance abuse, chronic cardiopulmonary disease, and immunosuppressive treatment.

Evidence of CHC was documented by anti-HCV antibodies or detectable HCV-RNA at least 6 months before screening. Presence of HCV infection was confirmed at screening by detectable HCV-RNA. Historical or pretreatment liver biopsy with evidence of fibrosis or inflammatory activity, or both, on local pathology report was requested for all patients before enrollment; however, a waiver was permitted for children ages 3–11 years who had an elevated alanine aminotransferase (ALT) within 1 year before screening. The central pathologist assessed biopsy slides using METAVIR fibrosis and activity scores. Liver steatosis was also graded in five categories: 0%, >0% to $\leqslant$5%, >5% to $\leqslant$32%, >32% to $\leqslant$66%, and >66%.

Treatment schedule

Treatment consisted of PEG-IFN alfa-2b (60 $\mu g/m^2$) once-weekly plus RBV (15 mg/kg/day). The dose of PEG-IFN alfa-2b used in this study was approximately equivalent to the dose licensed for adults (1.5 μg/kg once-weekly), based on calculated conversion to body surface area. The dose of RBV was previously determined to be the most effective dose when used with IFN alfa-2b in pediatric studies [13]. Because maximum RBV dose was not to exceed 1200 mg/day, patients with body weight >90 kg were excluded. All patients with genotype (G) 1 or G4, and those with G3 who had high baseline viral load ($\geqslant$600,000 IU/ml), were assigned to 48 weeks of treatment. Patients with <2 $\log_{10}$ drop in HCV-RNA at week 12 or detectable HCV-RNA at week 24 discontinued treatment and entered follow-up. All patients with G2 and patients with G3 who had low viral load (<600,000 IU/ml) were assigned to 24 weeks of treatment. All patients were followed for 24 weeks after treatment.

Efficacy assessment

HCV-RNA levels were determined at screening; treatment weeks 2, 4, 12, 24, 30, and 48; and follow-up weeks 4, 12, and 24. Plasma HCV-RNA was measured using a proprietary assay (TaqMan; Schering-Plough; lower limit of detection 125 IU/ml). Primary efficacy end point was SVR, defined as undetectable plasma HCV-RNA at 24 weeks after treatment. Secondary end points were rapid virologic response (RVR, defined as undetectable HCV-RNA at treatment week 4), early virologic response (EVR, defined as undetectable HCV-RNA at treatment week 12), and relapse (defined as undetectable HCV-RNA at the last treatment visit and detectable HCV-RNA at the last follow-up visit). Biochemical response was defined as normalization of ALT levels among patients with elevated ALT at baseline.

Safety assessments

Clinical assessments included physical examinations with vital signs, weight, and height measurements. Adverse events (AEs) were graded as mild, moderate, or severe.

The protocol contained strict guidelines for dose reduction or treatment discontinuation in the event of abnormalities in laboratory values. PEG-IFN alfa-2b dose reduction was required for neutrophil count $<750/mm^3$ or platelet count $<70{,}000/mm^3$. RBV dose reduction was required in patients with hemoglobin levels <10 g/dl. Discontinuation of both drugs was required for neutrophil count $<500/mm^3$, platelet count $<50{,}000/mm^3$, and if hemoglobin levels decreased <8.5 g/dl. For PEG-IFN alfa-2b and RBV, two-step dose reductions were used; PEG-IFN alfa-2b was first reduced to 40 $\mu g/m^2$ weekly. If the event failed to resolve adequately, the dose was further reduced to 20 $\mu g/m^2$ weekly. RBV was initially reduced to 12 mg/kg/day and then to 8 mg/kg/day, if needed.

Pharmacokinetic analyses are presented as supplementary material available online.

Statistical analysis

The primary efficacy variable was the proportion of patients who attained SVR. Carry-forward analysis was also performed. It included patients who had missing HCV-RNA data at 24 weeks after treatment but undetectable HCV-RNA at 12 weeks after treatment as sustained responders.

Results

Of 107 children enrolled, 67 children were age 3–11 years and 40 were adolescents age 12–17 years; 51 were boys and 56 were girls (Table 1). Pretreatment liver biopsy samples were assessed from 104 (97%) patients. Histology assessments showed that 13 (12.5%) patients had no fibrosis (METAVIR fibrosis score, F0), 88 (84.6%) had minimal fibrosis (F1), 2 (1.9%) had portal fibrosis with rare septae (F2), 1 (1%) had numerous septae (F3), and none had cirrhosis (Fig. 1). Most patients had mild (44%) or moderate (30%) liver inflammation, and 19 (18%) had severe inflammatory activity. Most patients had absent (71%) or $\leqslant$5% (22%) steatosis.

Enrolled patients per site are presented as supplementary material available online.

Sustained virologic response

Overall, SVR was attained by 65% (70/107) of all patients with responses similar in younger and older patients. Genotype was the main predictor of treatment outcome with SVR rates of 53%, 93%, 93%, and 80% in patients infected with G1, G2, G3,