

Treating Hepatitis C: Are Children the Same as Adults?

See “The combination of ribavirin and peginterferon is superior to peginterferon and placebo for children and adolescents with chronic hepatitis C,” by Schwarz KB, Gonzalez-Peralta RP, Murray KF, et al, on page 450.

Significant progress has been made in the management of hepatitis C virus (HCV) infection over the last decade. Combination treatment with pegylated interferon (PEG-IFN) plus ribavirin (RBV) represents the standard of care for the adult patient infected with chronic hepatitis C, producing sustained virologic response (SVR) in about half of persons treated. A number of host and viral factors that contribute to response to antiviral therapy have been identified in adults. Among viral factors, HCV genotype followed by pretreatment viral load are the most important predictors of SVR. Patients harboring genotypes 2 or 3 have substantially higher response rates than those with genotype 1, and those with pretreatment viral load levels $<2 \times 10^6$ copies/mL (800,000 IU/mL) are more likely to experience SVR. Additional predictors of antiviral response include histology (absence of fibrosis and significant steatosis being more favorable), lower body mass index, and younger age.¹ Comorbidities such as diabetes mellitus, insulin resistance, and HIV co-infection also negatively impact response rates.²⁻⁴ Race has been found to be an important determinant of response to therapy, with lower SVR rates among African Americans as compared with Caucasians. The recent identification of a polymorphism in the interleukin (IL)-28B locus on chromosome 19 as an exceptionally strong predictor of response to antiviral therapy, and may explain a large portion of the observed racial variation in response.⁵ However, we have learned also that, despite these advances, efforts to control HCV infection at a population level have been hampered by a lack of knowledge and awareness among health providers and the general public as well as by inadequate screening efforts leading to significant underdiagnosis.⁶

What is known about the management of HCV infection in children? The literature on pediatric hepatitis C is limited. In 1992, Ruiz-Moreno et al⁷ published their findings on a study of 12 children treated with recombinant IFN- α monotherapy. Later studies of pediatric HCV infection treatment with IFN were nonrandomized and included <50 patients each.⁸⁻¹⁰ In 2005, Gonzalez-Peralta et al¹¹ studied 118 children treated with a com-

bination of interferon alfa-2b plus RBV with 46% of patients achieving SVR. Subsequently, there have been studies evaluating the use of PEG-IFN for pediatric HCV infection, but the majority have been small in number and none have been randomized trials (Table 1). The results of one of the largest pediatric studies, an international multicenter trial, was recently published by Wirth et al.¹² A total of 107 children 3–17 years of age were treated with PEG-IFN alfa-2b (60 μ g/m² per week) and RBV (15 mg/kg per day) for 48 weeks (genotype [G]1, G4, or G3 with high viral load) or 24 weeks (G2, G3 with low viral load) in an uncontrolled trial. SVR was attained in 65% of all patients, but only in 53% of those with genotype 1. Baseline viral load was the main predictor of response in the G1 cohort. No differences were noted based on patient age. There were no serious adverse events related to antiviral therapy.

However, none of these investigations evaluated whether combination therapy is superior to PEG-IFN monotherapy in the treatment of HCV infected children. This is an important question, because RBV, as the authors argue, has been found to be teratogenic¹³ and embryotoxic¹⁴ in animals. In this issue of GASTROENTEROLOGY, Schwarz et al¹⁵ address this question by performing the only randomized, placebo-controlled trial of the safety and efficacy of PEG-IFN with and without RBV in children and adolescents with chronic hepatitis C, and did so in the largest pediatric treatment cohort published to date (PEDS-C). But perhaps even more significant is the fact that Schwartz et al explicitly ask whether children should be treated in the same manner as adults, highlighting the importance of potential differences and similarities in these 2 groups.

Schwarz et al compared children with chronic HCV infection, 5–18 years of age, who were randomly assigned for treatment with PEG-IFN alfa-2a (180 μ g/1.73 m² subcutaneously each week) and RBV (15 mg/kg per day in 2 divided doses) or PEG-IFN alfa-2a and placebo for 48 weeks. Most study participants had mild to moderate liver disease, 4% had bridging fibrosis, and 2% had cirrhosis. SVR was achieved in 59% of children treated with combination therapy versus 21% of those in the PEG-IFN alfa-2a plus placebo group. Among patients infected with HCV G1, 47% achieved SVR in the combination arm as opposed to only 17% in the PEG-IFN alfa-2a plus placebo group. When evaluating predictors of SVR, the investigators noted that combination therapy, HCV genotype other than 1, nonmaternal route of transmission, and

Table 1. Investigations of PEG-IFN With and Without RBV for the Treatment of Pediatric HCV Infection

Author/year	Study type	n	Treatment	Results	Adverse events
Zhang et al ²²	Open-label, uncontrolled (mixed genotypes)	54	PEG-IFN-alfa-2a (104 µg/m ² /wk); RBV (15-20 mg/kg/d)	SVR 87.9%	Pyrexia, fatigue, decreased appetite, skin rash
Kowala-Piaskowska et al ²³	Open-label, uncontrolled (G1 only)	20	PEG-IFN-alfa (not available); RBV (not available)	ETR 85%	Not reported
Schwarz et al ²⁴	Open-label, uncontrolled (G1 = 13; non-G1 = 1)	14	PEG-IFN-alfa-2a (BSA [m ²]/1.73 m ² × 180 µg)	SVR 43%	Pyrexia, fatigue, headache, nausea, vomiting, injection site reaction, no SAE
Kowala-Piaskowska et al ²⁵	Open-label, uncontrolled (mixed genotypes)	23	PEG-IFN-alfa-2a or 2b (2b:1.5 µg/kg; 2a:100 µg/m ²); RBV (15 mg/kg/d)	EVR 65.3%	Not reported
Jara et al ²⁶	Open-label, uncontrolled (mixed genotypes)	30	PEG-IFN-alfa-2b (1 mg/kg/wk); RBV (15 mg/kg/d)	SVR 50% (G1 and G4: 44%; G3: 100%)	Flu-like symptoms, weight loss, behavioral problems, leukopenia
Tajiri et al ²⁷	Retrospective survey (mixed genotypes)	37	PEG-IFN-alfa-2b (60 µg/m ² /wk); RBV (15 mg/kg/d)	SVR 81.8%	Lethargy; no SAE
Wirth et al ²⁸	Open-label, uncontrolled (mixed genotypes)	107	PEG-IFN-alfa-2b (60 µg/m ² /wk); RBV (15 mg/kg/d)	SVR 65% (G1: 53%)	Anemia, leukopenia, neutropenia, abdominal pain, nausea, vomiting, anorexia, arthralgias, myalgias, dizziness, headache, alopecia, fatigue, injection site erythema, pyrexia; no SAE
Sokal et al ²⁹	Open-label, uncontrolled (mixed genotypes: group A: G2/3; group B: G1/4/5/6)	65	PEG-IFN-alfa-2a (100 µg/m ² /wk); RBV (15 mg/kg/d)	EVR: 83% (group A); 57% (group B) ETR: 94% (group A), 57% (group B) SVR: 89% (group A), 57% (group B)	Fever, Flu-like symptoms, irritability, depression, change of mood, vomiting, abdominal pain, loss of appetite, dermatitis
Al Ali et al ³⁰	Open-label, uncontrolled (G4 only)	12	PEG-IFN-alfa-2b (1.5 mg/kg/wk); RBV (15 mg/kg/d)	SVR 75%	Flu-like illness, leucopenia, anemia, hypothyroidism

ETR, end-of-treatment response; EVR, early virologic response; SAE, serious adverse events; SVR, sustained virologic response.

female gender were strongly associated with response. A lower baseline HCV RNA level was among the most important predictors of response. No difference was observed between the combination and placebo groups for patients with HCV RNA <600,000 IU/L, although this group represented no more than 30% of the cohort. Response was associated also with the presence of moderate or marked hepatic inflammation and to the absence of steatosis. This investigation did not demonstrate an association between baseline fibrosis and SVR. Similarly, race or body mass index were not associated with SVR. However, it is important to note that this study was not designed to evaluate predictors of response; as such, the number of subjects within each of the relevant subgroups may have been insufficient to reach conclusions about certain variables. Details of the pathologic findings from children in this trial have been reported previously,¹⁶ demonstrating greater fibrosis among children who were overweight, which raises the question of the role of body mass index in the progression of HCV infection.

During the 2-year study period in PEDS-C, response proved to be durable. Durability of virologic response was

100% among the 82%–86% of SVR subjects who completed the 2-year follow-up evaluations. Interestingly, few children achieved viral clearance at 4 weeks of treatment, but all patients who did achieved SVR. There were 3 subjects who did not achieve viral clearance at week 12 of treatment (early virologic response), but did achieve SVR, in contrast with observations from the adult literature.^{17,18} Dose reductions were necessary in about one third of the entire cohort, and somewhat more frequently in the combination therapy arm. Overall, therapy was well tolerated and there were few serious adverse events.

As eluded to by Schwarz et al, children are not small adults. Most new cases of pediatric HCV infection are the result of maternal-to-infant transmission. What it means for a developing fetus or for a newborn to acquire HCV infection remains largely unknown. There are some suggestions that this mode of acquisition may be associated with more aggressive disease.¹⁹ Schwarz et al's study showed infection acquired in this manner was a strong negative predictor of response. However, more studies are needed to learn the differences between this and other modes of HCV acquisition in pediatric populations. Po-

tential effects on the developing body and brain should be considered, ideally balancing effects of therapy with those of the HCV itself. As we have learned from PEDS-C, discontinuation of treatment may not be indicated as a result of inability to achieve early virologic response in children, in stark contrast with adults, for whom this is a stopping rule. Female gender was significantly associated with SVR in PEDS-C; by contrast, the adult literature has not recognized this to be a major predictor of response to antiviral therapy. The basis for this difference in children may require further exploration. This investigation and others support the notion that children tolerate antiviral therapy better than adults, and this is an important factor to consider when making medical management decisions.

Understanding the differences between children and adults with respect to hepatitis C infection is not only relevant to pediatricians. Results of studies from HCV-infected adults are often confounded by comorbidities such as type 2 diabetes, alcoholic liver disease, cardiovascular diseases, and others. Children, on the other hand, most often lack these comorbidities. They represent a natural cohort that can help to elucidate our understanding of the pathogenesis of hepatitis C through assessment of direct viral effects, which in turn may inform the adult literature. Thus, knowledge about pediatric hepatitis C infection is not only essential for the proper management of affected children, but can also serve the HCV-infected community at large.

Unfortunately, evidence on the subject of HCV infection in children is limited for the moment. Important, well-established concepts in the treatment of adults with HCV infection have not been documented in the pediatric literature. The negative associations between African-American race and advanced hepatic fibrosis with SVR were not observed by Schwarz et al and have not been reported in pediatric studies, likely as a result of insufficient power among available investigations to answer these questions. The role of obesity as a factor accelerating liver disease in HCV infection and as a negative predictor of response among children and adolescents²⁰ should also be investigated in prospective trials. Despite a large body of literature on the metabolic consequences of HCV infection in adults, the answers to questions such as whether HCV induces insulin resistance, the role of insulin resistance in the natural history of HCV, or whether HCV leads to alterations in lipid metabolism in children have not been reported. Similarly, the effects of polymorphisms of the *IL28B* gene on response to antiviral therapy in children are not known.

Schwarz et al's investigation is an important step toward an improved understanding of pediatric HCV infection and its management, because it exemplifies the scientifically rigorous evidence that is much needed in

the field. However, more work needs to be done. The fact that the only randomized, placebo-controlled trial of PEG-IFN and RBV in children is published a decade after this became the standard of care for adults speaks for itself. Upcoming advances in the management of adult HCV infection that are currently under investigation should provide an impetus for equivalent research in sufficiently large pediatric cohorts now rather than later. The notion by some that treatment should be delayed or postponed in HCV infected children is predicated more on opinion than fact. At present, there are likely more questions than answers in reference to pediatric HCV infection. As the Institute of Medicine recently reported, a large percentage of HCV infected individuals is unaware of their condition⁶; in addition the majority of HCV-infected children have not been diagnosed.²¹ To make progress in the medical treatment of pediatric HCV infection, we must first have a better understanding of the natural history of this disease and the effects it has on the developing child. Introducing efficacious therapies will be important, but improving the effectiveness of available treatments will be essential for the management of this condition of important public health concern not only for children, but also for adults. Efforts to improve identification of infected cases will be critical to achieve these goals and will aid in improving our knowledge of pediatric HCV.

In conclusion, PEDS-C is a well-designed, randomized, placebo-controlled trial that demonstrates superior SVR rates for PEG-IFN alfa-2a with RBV as compared with PEG-IFN alfa-2a alone for the treatment of children infected with hepatitis C. The other important contribution of this study is that it highlights the uniqueness of the pediatric patient. So, are children the same as adults? "Yes," in that they benefit from combined therapy for HCV. "No," in some ways, including altered viral kinetics. "We don't know" in most ways. Efforts to accelerate trials in children will be essential to understand the key host differences between children and adults.

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Conflicts of interest

The authors disclose no conflicts.

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