

Hepatitis C Virus in Children: Deferring Treatment in Expectation of Direct-Acting Antiviral Agents

Esther Granot MD¹ and Etienne M. Sokal MD²

¹Division of Pediatrics, Kaplan Medical Center, Rehovot, and Hebrew University-Hadassah Medical School, Jerusalem, Israel

²Institut de Recherche Expérimentale et Clinique, Pôle Pédiatrie, Université Catholique de Louvain, and Service de Gastroentérologie et Hépatologie Pédiatrique, Cliniques Universitaires St Luc, Brussels, Belgium

ABSTRACT: The major route of hepatitis C virus (HCV) infection in the pediatric age group is vertical, with infection occurring in up to 5% of infants born to mothers positive for HCV-RNA. The natural course of pediatric HCV infection is characterized by a high rate of spontaneous clearance, an asymptomatic clinical course, and normal or mild histologic changes. Cirrhosis is reported in 1–2% of children, and progression to severe chronic liver disease and HCC occurs 20–30 years after infection. Treatment with pegylated interferon (Peg-IFN) + ribavirin results in a sustained viral response (SVR) reaching 100% in children with HCV genotypes 2 or 3 but only 45–55% in those infected with genotypes 1 or 4. Treatment is associated with adverse effects ranging from flu-like symptoms, myalgia, anemia and thrombocytopenia, to less commonly observed thyroid-related symptoms, alopecia, neuropsychiatric manifestations and possible long-term effects on growth. Ongoing trials with direct-acting antiviral agents in adults show promising results with treatment regimens of shorter duration and high tolerance. The next few years will likely see these advances introduced to the pediatric population as well. In the meantime, in children with HCV an expectant approach is advocated and treatment should be offered only to those at high risk for more severe, progressive disease.

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The major route of hepatitis C virus (HCV) infection in the pediatric age group is vertical, with infection occurring in up to ~5% of infants born to mothers positive for HCV-RNA. Risk factors shown to increase the possibility of HCV vertical transmission include co-infections with human immunodeficiency virus (HIV), intravenous drug use and elevated maternal HCV viral load. Immunoregulatory changes occurring during pregnancy, with impaired function of maternal CD8 cytotoxic T lymphocytes, facilitate vertical transmission of the virus. Currently, the parenteral route, via blood products, solid

organ or bone marrow transplantation, is responsible for only a minor fraction of children with HCV infection.

OUTCOME OF HCV INFECTION IN INFANCY AND CHILDHOOD

It is estimated that in children with vertically acquired HCV, 25–40% will undergo alanine aminotransferase (ALT) normalization and loss of HCV-RNA by the age of 2–3 years [1–3]. Spontaneous resolution can be achieved in up to 6–12% of infected children, as late as 7 years of age [1–4]. High ALT levels at onset seem to offer greater opportunity for biochemical remission and loss of viremia [2], with a potent inflammatory response preceding viral clearance [5]. Clearance was found to be significantly higher in infants infected with HCV genotype 3 [6]. In children infected via the parenteral route, HCV-RNA clearance is highly variable. In long-term follow-up studies of 25–30 years, clearance ranged from 11% in a cohort of infants infected by an HCV-RNA-positive blood donor [7] to 30–45% in cohorts similarly infected in early infancy via contaminated blood products during surgery [8,9]. Of those children in whom spontaneous viral clearance is not achieved, most (~80%) will be asymptomatic with normal or mildly elevated transaminases. However, 10–20% of HCV-infected children will have persistent elevation of transaminases and may manifest clinical signs of liver disease.

In a study including 504 children from 12 centers in Italy [6], 60% of whom had been infected by vertical transmission and 30% parenterally, most (~80%) of the children who had evidence of ongoing viral replication had normal or minimally elevated ALT levels. The remaining 20% had persistent elevation of ALT levels, some with hepatomegaly. Over a 10 year period, 2% had progressed to decompensated cirrhosis. Histologic changes in the majority of HCV-infected children are absent or mild over a long-term follow-up. In a group of 11 patients parenterally infected as babies and studied after 35 years, Casiraghi et al. [7] observed no fibrosis or only mild portal fibrosis in 9, while discrete or marked fibrosis were demonstrated in 2. In five of the patients, biopsies were repeated after 5 years revealing no histological changes compared to the previous biopsy in four and mild portal fibrosis in one patient whose biopsy had been previously normal. In 17 HCV-infected children studied by Vogt

and team [8] 20 years after cardiac surgery, the biopsies showed no histological signs of progressive liver damage. Similarly, over a follow-up of up to 21 years (mean 11 years) in 20 biopsies of 17 children with parenterally acquired HCV infection [10] and in 64 children with either vertical or parenteral HCV infection followed for a median period of 8 years [11], fibrosis was either absent or low grade.

Yet, some children do manifest more severe histological lesions. In the PEDS-C trial, of 121 children with a mean age of 9.8 years, most with vertically transmitted HCV genotype 1, 38% did have a moderate degree of liver inflammation and in 3% it was severe. Bridging fibrosis was observed in five children and two of the children had cirrhosis [12]. While some studies have failed to demonstrate a correlation between duration of infection and degree of fibrosis [11,12], others did provide evidence for a significant association between fibrosis scores and duration of disease. In a study of children from seven European centers, the fibrosis score was 1.5 ± 1.3 in children younger than 15 years and 2.3 ± 1.2 in older children, and the fibrosis score increased by 0.15 point per year of follow-up [13].

Thus, the natural course of pediatric HCV infection is characterized by:

- a high rate of early spontaneous clearance
- an asymptomatic clinical course (the majority of children are clinically well)
- histology showing that most children have no or only mild fibrosis, but evidence of insidious progression of liver disease on follow-up liver biopsies
- cirrhosis developing in 1–2% of children with chronic HCV
- progression to severe chronic liver disease and HCC occurring at least 20–30 years after infection.

Only a few cases of hepatocellular carcinoma (HCC) have been reported in adolescents. In adults, it has been estimated that progression of chronic liver disease ranging from chronic hepatitis to cirrhosis and occasionally to HCC may take 20–40 years and even longer [14].

Conditions associated with an increased risk of more severe disease include obesity, alcohol consumption and IV drug use, childhood cancer, immunosuppression and liver transplantation, congenital anemia requiring chronic transfusions, and co-infection with HIV/hepatitis B virus [15–19]. The increased worldwide prevalence of obesity among children and adolescents is a growing concern with serious consequences and comorbidities. In the PEDS-C trial, in 121 children aged 2–16 years (mean 9.8), overweight children

Spontaneous resolution of HCV infection occurs in ~40% of children during infancy and early childhood. Most infected children are asymptomatic with normal or mildly elevated transaminases and absent or minimal liver fibrosis

had more fibrosis than the non-overweight [12]. In a study of 123 children and teenagers with HCV infection (the majority genotype 1), overweight patients also manifested a higher

degree of fibrosis. Although in that study the association was not statistically significant, these observations do suggest that obesity adversely affects progression of chronic HCV liver disease. Furthermore,

patients with higher mean body mass index percentiles had a diminished response to either IFN or pegylated interferon (Peg-IFN) $\pm$ ribavirin therapy; among non-responders 42% were overweight compared to 19% of responders [15].

TREATMENT OF HCV INFECTION

Combined treatment with IFN α 2b or IFN α 2a and ribavirin has resulted in a sustained virological response (SVR) of 85–100% in children infected with HCV genotype 2 or 3, but only 35–50% in children infected with HCV genotype 1 [20–22]. As of 2008, Peg-IFN has been approved for use in children, but combination therapy with Peg-IFN α 2b or Peg-IFN α 2a plus ribavirin has failed to significantly increase SVR. In children with HCV genotype 2 or 3 infection the SVR achieved is 90–100% but has remained at ~45–55% in those with HCV genotype 1 infection [23–25]. A systematic review and meta-analysis included eight trials in which 438 children aged 3–18 years were treated with Peg-IFN α 2b or Peg-IFN α 2a and ribavirin [26]. In children with genotype 2/3 infection a SVR of 89% was observed, while in children with genotypes 1/4 infection the SVR reached 52% [Table 1]. In comparison, a meta-analysis of nine early pediatric trials using IFN monotherapy in 211 children reported a SVR of 27% for genotype 1/4 and 50% for genotype 2/3 [27]. Treatment with IFN and or IFN/ribavirin are accompanied by a number of adverse effects ranging from almost universal flu-like symptoms, headaches, myalgia and arthralgia to neutropenia, which occurs in up to 50% of patients, mainly during the first few weeks of treatment. Anemia, thrombocytopenia, alopecia, pruritus and thyroid-related symptoms are less commonly observed.

Most distressing are the neuropsychiatric manifestations that

have been associated with IFN therapy. Mood alterations, irritability, agitation and aggressive behavior have been noted in up to 30% of children. Depression, anxiety and suicidal ideation

have been reported in a small number of children [28,29].

Studies on the long-term effects of IFN plus ribavirin treatment on growth have yielded inconsistent results. Both weight loss and a decrease in growth velocity occur during the treatment period. However, while a compensatory weight gain does occur following termination of therapy [24,28], post-treatment

Currently approved treatment with Peg-IFN + ribavirin achieves a sustained virological response in only 45–55% of children infected with genotypes 1 & 4 and is associated with significant adverse effects

growth velocity is probably not fully compensatory. Sokal and colleagues [25] found follow-up height to be comparable to pre-treatment height percentiles, whereas in other studies by Jonas et al. [30] and Wirth et al. [28] height-for-age scores failed to return to baseline after 2 years of observation.

In view of the current SVR rate achieved in children infected with HCV genotype 1 and the substantial adverse effects during and after treatment, defining criteria for prediction of response to Peg-IFN + ribavirin therapy is imperative. A lower viral load has been suggested to be a positive predictive factor: polymerase chain reaction-RNA < 600,000 IU/ml [22,28,29]. A recent study in 82 children and adolescents concluded that interleukin (IL)-28B gene polymorphisms were the only predictors of response to IFN + ribavirin therapy. Interestingly, children with the single-nucleotide polymorphism associated with a higher response to therapy also had significantly higher baseline viral loads [31]. In adults, IL-28B polymorphism does not appear to influence the response to triple therapy with Peg-IFN + ribavirin and protease inhibitors. Thus, with the development of newer therapies, IL-28B receptor polymorphism may not prove useful in predicting response to therapy [32,33].

No significant association was demonstrated between treatment outcome and age, gender, route of infection (vertical vs. parenteral) and pretreatment ALT levels [11,31]. Furthermore, pretreatment liver histology was also not helpful in predicting response. It is noteworthy that most patients have low inflammatory activity and minimal fibrosis, precluding subgrouping of patients based on histopathologic findings.

NEW TREATMENT MODALITIES

Direct-acting antiviral agents (DAAs) have revolutionized the treatment of HCV infection. These drugs are specifically designed to inhibit three viral proteins: NS3/4A protease, NS5A protein and NS5B RNA-dependent polymerase. Trials in adults with either one of the two NS3/4A protease inhibitors telaprevir and boceprevir, in combination with Peg-IFN + ribavirin, have resulted in a SVR of 68–75% in genotype 1 treatment-naïve patients [32,33]. Dermatological adverse events and anemia have been reported to accompany treatment with telaprevir. Dysgeusia has been the most troubling side effect in patients treated with boceprevir. Newer NS3/4A protease inhibitors (simeprevir, danoprevir) given in combination with Peg-IFN + ribavirin achieve an even higher SVR of up to 93% in naïve genotype 1 patients, an SVR of 100% in genotype 4 patients and an SVR of 85% in prior relapsers [34,35]. The NS3/4A protease inhibitor simeprevir and NS5B RNA-dependent polymerase inhibitor sofosbuvir can reduce the length of antiviral treatment, improve response rate and allow for interferon-free regimens. Simeprevir plus sofosbuvir with or without ribavirin for either 12 or 24 weeks yielded a SVR of over 90% 12 weeks

Table 1. Selected IFN/Peg-IFN + ribavirin treatment trials in children with HCV

Author, year [ref]	No. studied	Treatment regimen	Sustained virological response (%)	
			HCV type 1/4	HCV type 2/3
Wirth, 2002 [21]	41	IFN2b + ribavirin	53	100
Gonzalez-Peralta, 2005 [22]	118	IFN2b + ribavirin	36	84
Wirth, 2005 [23]	62	Peg-IFN2b + ribavirin	48	100
Wirth, 2010 [28]	107	Peg-IFN2b + ribavirin	53	93
Schwarz, 2011 [29]	55	Peg-IFN2a + ribavirin	47	80
Jara, 2008 [24]	30	Peg-IFN2b + ribavirin	44	100
Sokal, 2010 [25]	65	Peg-IFN2a + ribavirin	57	89
Wisniewska-Ligier, 2013	79	Peg IFN-2b-ribavirin	44	
Druyts, 2013 a meta-analysis [26]	438	Peg-IFN2a or 2b + ribavirin	52	89

after stopping treatment (SVR12) in treatment-naïve or previous non-responders with genotype 1 chronic HCV. Common adverse effects were mild and included fatigue, headache and nausea [36]. Other studies in patients with HCV genotype 1, based on all-oral treatment regimens with a combination of three or four direct antiviral agents, ABT-450 and ritonavir (protease inhibitors), ombitasvir (a NS5A inhibitor), dasabuvir (a non-nucleoside polymerase inhibitor), with or without ribavirin, resulted in high rates of SVR12 (> 95%), were well tolerated and had an excellent safety profile [37,38]. In a recent study using a fixed dose combination of sofosbuvir and the NS5A inhibitor ledipasvir alone or with ribavirin administered for 8–12 weeks, 95–100% of patients with genotype 1 infection achieved a SVR12 irrespective of treatment history or the presence of compensated cirrhosis [39].

Thus, the field of hepatitis C therapy is evolving rapidly, and current trends indicate that the era of simple oral treatment regimens with high success rates and good tolerability is already here. Two new IFN-free, DAA-based combinations were approved in late 2014/early 2015 in the United States and Europe. The combination of sofosbuvir (400 mg) plus ledipasvir (90 mg) in one single pill, daily, with or without ribavirin is approved for genotypes

1, 3 and 4. In genotype 1 patients this combination, with or without ribavirin, has yielded an SVR of 99% and 97% after 12 weeks of treatment and 98% and 99% after 24 weeks,

respectively [40]. The triple combination of ritonavir-boosted paritaprevir (a second-wave, first-generation NS3/4A protease inhibitor) and ombitasvir, in one single pill (50 mg/75 mg/12.5 mg per pill, 2 pills daily) plus dasabuvir in another pill (250 mg, 2 pills daily), with or without ribavirin, is approved for HCV genotype 1. Indeed, an all-oral, pan-genotypic IFN-free treatment regimen, the holy grail of chronic HCV treatment, is today a reality.

We can confidently expect that treatment with these new antiviral agents will similarly become available for the pediatric

New all-oral treatment modalities are already available in adults and are expected to be introduced in children in the near future

age group in the near future. A phase 2 open-label multicenter trial is currently ongoing to determine the safety and efficacy of a fixed dose combination of ledipasvir/sofosbuvir, administered for 12 weeks, in children and adolescents. In the meantime, should children with chronic HCV infection be treated with currently approved medication, i.e., the combination of Peg-interferon and ribavirin? Given the high spontaneous clearance rate in infancy and early childhood, we recommend that children not be treated before the age of 5–6 years. In children infected with HCV genotype 2 or 3, standard of care treatment with Peg-IFN + ribavirin for 24 weeks attains an SVR of up to 100%. However, in view of the adverse affects of interferon-based treatment, we believe that treatment be considered based solely on the degree of liver disease progression and individual circumstances, such as adolescents about to graduate from high school and wanting to undergo treatment while still residing at home. In others, treatment can be deferred until all-oral DAA regimens become available. In children infected with HCV genotype 1 or 4 the SVR attainable with the current standard of care, Peg-IFN + ribavirin for up to 48 weeks, is expected to reach ~50%. Except for a subgroup of patients at high risk for a rapid more severe progression of liver disease, the natural history of the disease in childhood is mild and slow to evolve. Since novel, highly effective, all-oral treatment options with relatively few side effects and short duration of therapy are expected in the foreseeable future, a conservative approach is urged and treatment should be limited only to those children with the more active disease.

Correspondence

Dr. E. Granot

Division of Pediatrics, Kaplan Medical Center, P.O. Box 1, Rehovot 76100, Israel
email: Ettie_G@clalit.org.il

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