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

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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 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.

KEY WORDS: hepatitis C virus (HCV), sustained viral response (SVR), interferon (IFN), direct-acting antiviral agent (DAA)

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 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) ± ribavirin therapy; among non-responders 42% were overweight compared to 19% of responders [15].

**TREATMENT OF HCV INFECTION**

Combined treatment with IFNa2b or IFNa2a 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-IFNa2b or Peg-IFNa2a 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-IFNa2b or Peg-IFNa2a 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
growth velocity is probably not fully compensatory. Sokal and colleagues [25] found follow-up height to be comparable to pretreatment 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 (DAAAs) 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-naive 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 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-490 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

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

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

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References

**Capsule**

**Inflammasomes take the wheel of unfortune...**

Cells require microbial ligand binding to sense pathogens. Binding to the family of NOD-like receptors triggers the assembly of large protein signaling complexes called inflammasomes, leading infected cells to die and produce inflammatory mediators. Hu et al. and Zhang et al. used cryo-electron microscopy to uncover the structural and biochemical basis of two such receptors: NAIP2, which directly binds microbial ligands, and NLRC4, a protein functioning directly downstream. A self-propagating activation mechanism of downstream inflammasome signaling starts with one molecule of NAIP4 directly binding its microbial ligand. NAIP4 then catalyzes the activation of 10 to 12 NLRC4 molecules to form a wheel-like structure.

_Science_ 2015; 350: 399, 404
Eitan Israeli

**Capsule**

**The Ro60 autoantigen binds endogenous retroelements and regulates inflammatory gene expression**

Autoantibodies target the RNA binding protein Ro60 in systemic lupus erythematosus (SLE) and Sjögren's syndrome. However, it is unclear whether Ro60 and its associated RNAs contribute to disease pathogenesis. Huang et al. catalogued the Ro60-associated RNAs in human cell lines and found that among other RNAs, Ro60 bound an RNA motif derived from endogenous Alu retroelements. Alu transcripts were induced by type I interferon and stimulated pro-inflammatory cytokine secretion by human peripheral blood cells. Ro60 deletion resulted in enhanced expression of Alu RNAs and interferon-regulated genes. Anti-Ro60-positive SLE immune complexes contained Alu RNAs, and Alu transcripts were up-regulated in SLE whole blood samples relative to controls. These findings establish a link among the lupus autoantigen Ro60, Alu retroelements, and type I interferon. Short interspersed nuclear elements (SINEs) are short DNA sequences (< 500 bases) that represent reverse-transcribed RNA molecules originally transcribed by RNA polymerase III into tRNA, 5S ribosomal RNA, and other small nuclear RNAs. The mechanism of retrotransposition of these elements is more complicated than LINEs, and less dependent solely on the actual elements that they encode. SINEs do not encode a functional reverse transcriptase protein and rely on other mobile elements for transposition. In some cases they may have their own endonuclease that will allow them to cleave their way onto genome, but the majority of SINEs integrate at chromosomal breaks by using random DNA breaks to prime reverse transcriptase. The most common SINEs in primates are called Alu sequences. Alu elements are approximately 350 base pairs long, do not contain any coding sequences, and can be recognized by the restriction enzyme Alul (hence the name).

_Science_ 2015; 350: 455
Eitan Israeli

“Love does not consist in gazing at each other, but in looking outward together in the same direction”

Antoine de Saint-Exupery (1900-1944), French aristocrat, writer, poet, and pioneering aviator. He won several literary awards in France as well as the U.S. National Book Award. He is best remembered for his novella The Little Prince.

“Failure is the condiment that gives success its flavor”

Truman Capote (1924-1984), American novelist, screenwriter, playwright, and actor, many of whose short stories, novels, plays, and non-fiction are recognized literary classics, including Breakfast at Tiffany’s and the true crime novel In Cold Blood.