Guidance for Clinical Trials for Children and Adolescents with Chronic Hepatitis C

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**Abstract**
Currently, most children with chronic hepatitis C are infected vertically, have a low natural seroconversion rate and carry a lifetime risk of cirrhosis and cancer. Affected children are usually asymptomatic and histological findings are mild with a low risk of progression, although 5% develop significant liver disease in childhood.

The use of combination treatment with pegylated interferon-alpha and ribavirin has changed the outcome and prognosis for this disease with approximately 60% of children achieving sustained viral clearance. Combination therapy is not ideal for children because pegylated interferon is administered subcutaneously, impairs growth velocity, and both interferon and ribavirin have significant side effects which affect compliance. In addition, approximately 50% of children infected with genotype 1 do not respond to therapy. Thus, further treatment options are required including improvement in dosing, reducing the length of treatment and evaluation of new drugs such as protease inhibitors which could be more effective for patients infected with genotype 1.

The primary goal of treatment is to eradicate the infection. Future clinical trial design should ensure that any new drugs should demonstrate non inferiority to the present standard regimen in both children and adults. The measure for documenting substantial improvement above current therapy should be increased viral clearance rate or the same clearance rate, with a shorter duration of treatment and/or less side effects. We do not believe there is any need for a placebo arm, because approved therapy is available and new treatments can be compared to current therapy.
Safety measures should include the standard recommended laboratory investigations, growth parameters, quality of life or psychological measures and a requirement for long-term follow-up for up to 5 years.

**Key words:** chronic hepatitis C, children and adolescents, treatment, clinical trials, peginterferon, ribavirin

The guidance is the result of a consensus meeting of a working group in November 2009 consisting of members and experts of the ESPHAN Hepatology committee and EMA: Stefan Wirth, Deirdre Kelly, Etienne Sokal, Piotr Socha, Giorgina Mieli-Vergani, Anil Dhawan, Florence Lacaille for ESPGHAN; Agnès Saint Raymond, Sophie Olivier and Jan Taminiau from EMA
Background

In adults treatment guidelines for chronic hepatitis C (HCV) infection are based on a large number of published natural history studies and randomized controlled trials (RCT). There are less data available regarding the epidemiology, spontaneous course and treatment of chronic hepatitis C in children and adolescents. Initially, most guidelines recommended children to be managed and treated in a similar way as adults, although recent data suggest this may no longer be appropriate. Some experts recommend postponing treatment until adulthood because children are asymptomatic and have mild liver disease. Recently, several published open labelled treatment trials have demonstrated significant efficacy and safety of HCV therapy in children and adolescents using either interferon-alpha2b or peginterferon-alpha2b in combination with ribavirin, which resulted in official approval of this treatment regimen by FDA and EMA (1-5). There is now considerable experience with peginterferon-alpha2a in combination with ribavirin in children (6, 7). As in adults, sustained viral response (SVR) depends on genotype. Patients infected with genotype 2 and 3 respond significantly better than those with genotype 1 or 4 who only have response rates of 50% (5, 7). Therefore, half of treated patients remain chronic virus carriers with a risk of progressive liver disease(8, 9) so there are compelling reasons to improve current treatment options.

Epidemiology and spontaneous viral clearance

The prevalence of HCV in children in developed countries ranges between 0.1% - 0.4% (10-12). During the last ten years the predominant mode of viral hepatitis C transmission has become vertical infection. In developed countries, contamination through transfusion or health care is exceedingly rare, although it may remain frequent in developing countries. The rate of perinatal transmission from an infected
mother to her child ranges from 2 to 5% and is now the nearly exclusive mode of infection in Western countries (13, 14). In the United Kingdom the prevalence of HCV in pregnant women was 0.16% (10). In Scotland the prevalence ranged between 0.29 – 0.4% depending on age (15). From France a 0.53% HCV RNA prevalence of the young population was reported (16). Seroprevalence of antibody to HCV in the United States was 0.4% (17). Given a perinatal transmission rate of approximately 4% in HCV RNA positive mothers and an annual birth rate of 4.4 million newborns in North America and 5 millions in Europe, there could be an estimated number of at least 530 - 600 new unavoidable infections annually in infants for these industrialized regions. In case of vertical infection the chronicity rate is extremely high (18).

Spontaneous viral clearance after HCV infection in children seems higher in parenterally infected individuals and may reach 35-45% up to adolescence age (19, 20). However, viral clearance in vertically infected children seems to be dependent on the genotype and was found to range from 2.4-25% (13, 21, 22). In contrast, children infected with genotype 3 had a higher spontaneous clearance rate than those infected with genotype 1. Beyond the age of 4 years spontaneous viral clearance became unlikely (22).

**Chronic HCV infection**

It is well documented that HCV infection in children is clinically asymptomatic. Histological findings are usually mild and the risk of severe complications is low. Nevertheless, despite the favourable prognosis during the first and second decade of life, approximately 4-6% of children have evidence of advanced liver fibrosis or cirrhosis (8, 23). Large liver transplantation units have reported on children who needed liver transplantation due to progressive HCV infection (24). In a lifetime, the risk of developing cirrhosis is about 20%, which is influenced by alcohol consumption,
while the risk of hepatocellular carcinoma is based on developing cirrhosis 2-5% (25). However, these data are from adults and there is no valid information about long-term course of vertically infected children. A very recent study in pediatric patients cured of malignancy with chronic hepatitis C documented liver cirrhosis in 5% after three decades of observation (26).

**Treatment of chronic hepatitis C**

Initially, treatment of chronic hepatitis C in children and adolescents was based on an alpha-interferon monotherapy with multiple dosing regimen yielding a sustained viral response rate from 0 to 76% (27). 19 studies using alpha-interferon have been published between 1992 and 2003 (28-46). With increasing experience alfa-interferon monotherapy (injections thrice weekly) showed a rather poor response and ribavirin was added. 6 studies were published between 2000-2005 and demonstrated a SVR from 27 to 64% (1, 3, 45, 47-49). The stratification according to genotypes revealed a very good response (> 80%) in patients with genotype 2 and 3 and a SVR of approximately 36 - 53% in those with genotype 1. FDA and EMA approved interferon-alpha2b (3 Mio U, thrice a week) in combination with ribavirin (15 mg/kg per day).

Peginterferon in combination with ribavirin became the standard of care for adults with chronic hepatitis C. Advantages were better SVR, reduced injection frequency to once per week and a better side effect profile. Subsequently the therapy was evaluated in children and adolescents and the results of 6 trials have been reported up to date (2, 4-7, 50). SVR in patients with genotype 1 from 5 trials with more than 30 patients ranged from 44% to 59%. SVR in children with genotype 2 and 3 was more than 90%. 3 trials used peginterferon-alpha2b and 2 used peginterferon-alpha2a. The level of aminotransferases or histological findings by liver biopsy did
not correlate with SVR. In one study, 32% of children with genotype 1 and high viral load (>600,000 U/l) and 73% with low viral load (<600,000 U/l) achieved SVR (5). Peginterferon-alpha2b (60 µg/m² per week) and ribavirin (15 mg/kg per day) were approved by FDA (2008) and EMA (2009). Recommendations are that:- patients with genotype 1 and 4 should be treated for 48 weeks, with treatment discontinued at 6 months if there has been no viral response. Patients with genotype 2 and 3 should be treated for 24 weeks. The majority of treated children and adolescents will tolerate peginterferon and ribavirin quite well. Most adverse events were mild to moderate, although dose reductions of both drugs were required; the rates of discontinuation were low in all trials published. Severe psychiatric side effects were rare in prepubertal individuals, but thyroid dysfunction and transient growth impairment were reported (1, 5). Follow-up studies are in progress to evaluate long-term sequelae.

In summary, despite considerable progress in the treatment of children with chronic hepatitis C, in approximately half of patients with genotype 1, which represent the vast majority of infected individuals, treatment remains unsuccessful. The need for subcutaneous administration of pegylated interferon and the range of significant side effects with both interferon and ribavirin mean that further improvement in terms of dosing, reducing the length of treatment and evaluation of new drugs such as protease inhibitors is required.

**Rationale for further clinical trials for hepatitis C in children**

Current treatment is demanding with respect to parenteral administration, the range of side effects and patients’ compliance and its efficacy against genotype 1 is suboptimal.
Eradication of childhood HCV infection is desirable because children with chronic hepatitis C carry a lifetime risk of cirrhosis and cancer. The risk is probably not linear, and may be strongly influenced by environmental factors. However, affected children further expand the pool of hepatitis C carriers in the population, and hence participate in viral transmission. Importantly, children may feel stigmatized by their friends, and develop serious psychological problems, resulting in reduced quality of life. Additionally educational problems may rise with the risk of restraining their career choices by the infection, especially in the health field.

Moreover, therapy may be more efficient in children, due to the general absence of co-morbidities or intoxications. Current standard of care regimens using peginterferon in combination with ribavirin are long, relatively toxic and expensive. New protocols, either shorter, or with different drugs, are thus desirable.

Aims and criteria for treatment of hepatitis C in children

The primary goal of treatment is to eradicate the infection, in order to prevent late complications. Hence, the aim is not the treatment of an ongoing liver disease, but the prevention of a future one.

All children with chronic hepatitis C with active infection with a measurable level of HCV- RNA should be considered for treatment. Although neither the level of aminotransferases nor of HCV-RNA predicts the long term outcome, these criteria should be included in the analysis of the results as SVR might be better in individuals with genotype 1 who have a lower viral load (5).

Histology: We do not feel that liver histology is a useful entry criterion, as children generally do not have severe lesions. However, as steatosis is a prognostic factor for treatment response in adults, and is partly related to HCV infection itself as well as to
body weight, it would be desirable to perform a liver biopsy at the beginning of a trial, as a baseline and to include measures of fibrosis/steatosis in the analysis of the results (51, 52).

Endpoints: The primary endpoint should be sustained viral response (SVR) which is defined as persistent HCV RNA loss more than six months after cessation of treatment, anticipating eradication of the chronic HCV infection. A secondary endpoint would be normalization of aminotransferases.

**Design of clinical trials**

**Study drugs:** The drug to be tested should have demonstrated non inferiority to the present standard treatment in adults and children (pegylated interferon-alpha in combination with ribavirin). We do not feel that there is a need for a placebo arm, because approved effective therapy for children and adolescents is available and new treatments could be compared to current therapy. The test drug could be used in triple combination with pegylated interferon and ribavirin, or as monotherapy. New treatment options should primarily focus on patients infected with genotype 1 because of the relative lack of efficacy of current therapy. Improved efficacy could be evaluated as an increased viral clearance rate (e.g. >65%) in those patients. Alternatively, new treatment regimens could achieve the same viral clearance rate, but with a shorter duration of treatment or with less side effects.

**Inclusion criteria:** All children with chronic hepatitis C, defined as persistence of viral replication with positive HCV RNA for more than 6 months are eligible independent of the mode of transmission and the level of aminotransferases prior treatment. Treatment is not indicated before the age of three years because of safety reasons, and to allow for the possibility of spontaneous viral clearance. Trial
protocols should stratify patients according to genotype 1 and 4, and 2 and 3, respectively. Two age groups (3 – 10 years and 10 – 18 years) should be separately documented and analysed. In view of the effect on final height, treatment during rapid growth spurts or puberty should be avoided if possible. Additional factors influencing SVR such as mode of infection, sex, aminotransferase levels and histological grading of fibrosis, inflammation and steatosis (51, 52) should be recorded. Female adolescents should be advised to protect against pregnancy.

Children with previous treatment failure could be included 2 years after the end of treatment to allow for delayed seroconversion and/or the effects of the previous medication. Individuals with significant co-morbidities interfering with liver function such as co-infection with HIV, chronic hepatitis B, hepatotoxic treatments, or other liver diseases, should be not be treated in clinical trials.

The recommended necessary baseline investigations before treating patients with chronic hepatitis C in a clinical trial are summarized in table 1. A baseline liver biopsy is recommended although histological inflammatory activity and fibrosis is likely to be mild but measures of steatosis may be useful as discussed above. Table 2 demonstrates two internationally established scores, which could be used to assess fibrosis and inflammation (51, 52).

Surrogate markers of steatosis such as findings of ultrasonography, MRI or Fibroscan® are not generally available and are not standardized. Thus, for a more reliable analysis of the results it is desirable to have a liver biopsy at the beginning of a clinical trial. Since insulin resistance is also a factor associated with response to treatment in adults, determination of HOMA is useful at the beginning and end of the treatment. Iron load has been related in adults to a more severe disease (53). Therefore the determination of serum ferritin levels is a meaningful marker for the analysis of results. Due to possible transient growth inhibition of interferons,
evaluation of growth parameters including z-scores for height and weight, growth velocity needs to be performed on a regular basis. Bone age in children > 7 years at the beginning and end of treatment may be a guide to estimated final height.

The recommended investigations and repeat frequency during treatment are shown in table 3. The decrease of HCV RNA during 4, 8 and 12 weeks after the initiation of treatment are evaluated and included in the analysis of the results. Patients with persistence of positive HCV RNA at 6 months, irrespective of genotype should stop treatment, because SVR is unlikely.

5 year follow-up after cessation of treatment is recommended and includes the measurement of standard blood tests, liver function tests and quantitative HCV RNA at 6 months and then annually to document sustained viral response. Growth and pubertal development should be assessed every six months and bone age at the end of treatment. Other tests may be necessary depending on the safety profile of each test drug.

Conclusion

We have summarized the rationale, indications for treatment, baseline investigations and safety parameters to be considered when designing future clinical trials of chronic viral hepatitis C in children. We hope they will be of value to guide clinicians, the regulatory authorities and the pharmaceutical industry.
Table 1. Recommended baseline investigations before HCV treatment

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<thead>
<tr>
<th>Clinical examination</th>
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<tr>
<td>Physical and neuropsychiatric examination</td>
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<tr>
<td>Tanner pubertal stage</td>
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<tr>
<td>Evaluation of growth parameters, z-scores for height and weight, BMI, waist circumference</td>
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<td>Description of co-morbidities</td>
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<th>Morphologic investigations</th>
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<tr>
<td>Liver Ultrasound</td>
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<td>Liver histology – assessed by Ishak or Metavir scores</td>
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<td>Bone age (&gt; 7 years of age)</td>
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<tr>
<th>Laboratory tests</th>
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<tr>
<td>Complete red and white blood count, reticulocytes, ALT, AST, gammaGT, AP, bilirubin, albumin, coagulation</td>
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<tr>
<td>Alpha-feto protein</td>
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<tr>
<td>BUN, creatinine, Immunoglobulins, autoantibodies (ANA; LKM1), Ferritin, TSH, thyroid-antibodies,</td>
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<tr>
<td>HOMA index, Pregnancy test</td>
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<td>Anti-HCV, quantitative HCV RNA, genotype</td>
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Table 2: Comparison of histological staging using Ishak and Metavir scores

<table>
<thead>
<tr>
<th></th>
<th>No Fibrosis</th>
<th>Mild Fibrosis</th>
<th>Moderate to severe fibrosis</th>
<th>Cirrhosis</th>
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</thead>
<tbody>
<tr>
<td><strong>ISHAK</strong></td>
<td>0</td>
<td>1</td>
<td>2,3&amp;4</td>
<td>5&amp;6</td>
</tr>
<tr>
<td><strong>META VIR</strong></td>
<td>0</td>
<td>1</td>
<td>2&amp;3</td>
<td>4</td>
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<tr>
<td>Parameter</td>
<td>Repeat frequency</td>
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<tr>
<td>Physical and neuropsychiatric examination</td>
<td>Every visit</td>
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<tr>
<td>Tanner pubertal stage</td>
<td>Every 3 months</td>
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<tr>
<td>Evaluation of growth parameters, z-score for height and</td>
<td>Every 3 months</td>
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<tr>
<td>weight, BMI, waist circumference</td>
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<tr>
<td>Growth velocity</td>
<td>Every 6 months</td>
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<tr>
<td>Bone age</td>
<td>End of trial</td>
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### Laboratory tests

| Complete red and white blood count, Alb, ALT, AST, gammaGT, AP, bilirubin, coagulation | Every month during the first 3 months, then every 3 months |
| Reticulocytes, albumin, BUN, creatinine, immunoglobulins, autoantibodies (ANA; LKM1), ferritin, TSH, thyroid-antibodies | Every 3 - 6 months |
| Quantitative HCV RNA,                                                      | 4, 8, 12 weeks, then every 3 months |
| HOMA index                                                               | End of treatment                  |
References


