

# Guidance for Clinical Trials for Children and Adolescents With Chronic Hepatitis C

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## ABSTRACT

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 adverse effects that affect compliance. In addition, approximately 50% of children infected with genotype 1 do not respond to therapy. Thus, additional treatment options are required including improvement in dosing, reduction in 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. The future clinical trial design should ensure that any new drugs demonstrate noninferiority to the present standard regimen in both children and adults. The measure for documenting substantial improvement above present therapy should be increased viral clearance rate or the same clearance rate, with a shorter duration of treatment and/or fewer adverse effects. We do not believe there is any need for a placebo arm because approved therapy is available and new treatments can

be compared with present 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:** children and adolescents, chronic hepatitis C, clinical trials, peginterferon, ribavirin, treatment

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## BACKGROUND

In adults, treatment guidelines for chronic hepatitis C virus (HCV) infection are based on a large number of published natural history studies and randomized controlled trials. There are fewer 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 that 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-label treatment trials have demonstrated significant efficacy and safety of HCV infection therapy in children and adolescents using either interferon- $\alpha$  2b or peginterferon- $\alpha$  2b in combination with ribavirin, which resulted in official approval of this treatment regimen by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) (1–5). In addition, there is now considerable experience with peginterferon- $\alpha$  2a 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 the treated patients remain chronic virus carriers with a risk of progressive liver disease (8,9), so there are compelling reasons to improve the present treatment options.

## EPIDEMIOLOGY AND SPONTANEOUS VIRAL CLEARANCE

The prevalence of HCV infection in children in developed countries ranges between 0.1% and 0.4% (10–12). During the last 10 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, but 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 infection in pregnant women was 0.16% (10). In Scotland the

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prevalence ranged between 0.29% and 0.4% depending on age (15). From France a 0.53% HCV infection RNA prevalence of the young population was reported (16). Seroprevalence of antibody to HCV infection in the United States was 0.4% (17). Given a perinatal transmission rate of approximately 4% in HCV infection, RNA-positive mothers, and an annual birth rate of 4.4 million newborns in North America and 5 million in Europe, there could be an estimated 530 to 600 new unavoidable infections annually in infants for these industrialized regions. In cases 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% to 45% up to adolescence (19,20). However, viral clearance in vertically infected children seems to be dependent on the genotype and was found to range from 2.4% to 25% (13,21,22). In contrast, children infected with genotype 3 had a higher spontaneous clearance rate than those infected with genotype 1. Beyond age 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 decades of life, approximately 4% to 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, whereas the risk of hepatocellular carcinoma is based on developing cirrhosis at 2% to 5% (25). However, these data are from adults and there is no valid information about the long-term course of vertically infected children. A recent study in pediatric patients cured of malignancy with chronic hepatitis C documented liver cirrhosis in 5% after 3 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 an SVR rate from 0% to 76% (27). Nineteen studies using  $\alpha$ -interferon have been published between 1992 and 2003 (28–46). With increasing experience  $\alpha$ -interferon monotherapy (injections thrice weekly) showed a rather poor response, and ribavirin was added. Six studies were published between 2000 and 2005 and demonstrated an SVR from 27% to 64% (1,3,45,47–49). The stratification according to genotypes revealed a good response (>80%) in patients with genotype 2 and 3 and an SVR of approximately 36% to 53% in those with genotype 1. FDA and EMA approved interferon- $\alpha$  2b (3 Mio U, thrice per week) in combination with ribavirin (15 mg · kg<sup>-1</sup> · day<sup>-1</sup>).

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 adverse effect profile. Subsequently, the therapy was evaluated in children and adolescents and the results of 6 trials have been reported (2,4–7,50). SVR in patients with genotype 1 from 5 trials with >30 patients ranged from 44% to 59%. SVR in children with genotype 2 and 3 was >90%. Three trials used peginterferon- $\alpha$  2b, and 2 used peginterferon- $\alpha$  2a. The level of aminotransferases or histological findings by liver biopsy did not correlate with SVR. In 1 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- $\alpha$  2b (60  $\mu$ g · m<sup>-2</sup> · week<sup>-1</sup>) and ribavirin (15 mg · kg<sup>-1</sup> · day<sup>-1</sup>) were approved by the FDA (2008) and the 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 well. Most adverse events were mild to moderate, although dose reductions of both drugs were required; the rates of discontinuation were low in all published trials. Severe psychiatric adverse effects were rare in prepubertal individuals, but thyroid dysfunction and transient growth impairment were reported (1,5). Follow-up studies to evaluate long-term sequelae are in progress.

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

### RATIONALE FOR FURTHER CLINICAL TRIALS FOR HEPATITIS C IN CHILDREN

Present treatment is demanding with respect to parenteral administration, the range of adverse 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. In addition, educational problems may rise with the risk of restricting 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 comorbidities or intoxications. The present 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 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 because SVR may 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 because children generally do not have severe lesions. However, because 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 SVR, which is defined as persistent HCV-RNA loss more than 6 months after cessation of treatment, anticipating eradication of the chronic HCV infection. A secondary endpoint should be normalization of aminotransferases.

## DESIGN OF CLINICAL TRIALS

### Study Drugs

The drug to be tested should have demonstrated noninferiority 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 with present therapy. The test drug could be used in triple combination with pegylated interferon and ribavirin or as monotherapy.

New treatment options should focus primarily on patients infected with genotype 1 because of the relative lack of efficacy of present therapy. Improved efficacy could be evaluated as an increased viral clearance rate (eg, >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 adverse effects.

### Inclusion Criteria

All of the 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 before treatment. Treatment is not indicated before age 3 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 comorbidities interfering with liver function, such as co-infection with HIV, chronic hepatitis B, hepatotoxic treatments, or other liver diseases, should 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 are likely to be mild, but measures of steatosis may be useful as discussed above. Table 2 demonstrates 2 internationally established scores that could be used to assess fibrosis and inflammation (51,52).

TABLE 1. Recommended baseline investigations before HCV infection treatment

Clinical examination
Physical and neuropsychiatric examination
Tanner pubertal stage
Evaluation of growth parameters, z scores for height and weight, BMI, waist circumference
Description of comorbidities
Morphological investigations
Liver ultrasound
Liver histology—assessed by Ishak or Metavir scores
Bone age (older than 7 years)
Laboratory tests
Complete red and white blood cell count, reticulocytes
ALT, AST, $\gamma$ -GT, AP, bilirubin, Alb, coagulation
$\alpha$ -Fetoprotein
BUN, creatinine
Immunoglobulins, autoantibodies (ANA; LKM 1),
Ferritin, TSH, thyroid antibodies
HOMA index
Pregnancy test
Anti-HCV, quantitative HCV-RNA, genotype

Alb = albumin; ALT = alanine aminotransferase; ANA = anti-nuclear antibody; AP = alkaline phosphatase; AST = aspartate aminotransferase; BMI = body mass index; BUN = blood urea nitrogen;  $\gamma$ -GT = gamma-glutamyl transferase; HCV = hepatitis C virus; HOMA = homeostasis model assessment; LKM = liver-kidney microsomal antigen; TSH = thyroid-stimulating hormone.

Surrogate markers of steatosis such as findings of ultrasonography, magnetic resonance imaging, 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. Because insulin resistance is also a factor associated with response to treatment in adults, determination of homeostatic model assessment index 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. Because of possible transient growth inhibition of interferons and evaluation of growth parameters including z scores for height and weight, growth velocity needs to be performed regularly. Bone age in children older than 7 years at the beginning and the 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.

Five-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

TABLE 2. Comparison of histological staging using Ishak and Metavir scores

	No fibrosis	Mild fibrosis	Moderate to severe fibrosis	Cirrhosis
Ishak	0	1	2, 3, and 4	5 and 6
Metavir	0	1	2 and 3	4

TABLE 3. Recommended investigations during HCV treatment

Parameter	Repeat frequency
Physical and neuropsychiatric examination	Every visit
Tanner pubertal stage	Every 3 mo
Evaluation of growth parameters, z score for height and weight, BMI, waist circumference	Every 3 mo
Growth velocity	Every 6 mo
Bone age	End of trial
Laboratory tests	
Complete red and white blood cell count, Alb, ALT, AST, $\gamma$ -GT, AP, bilirubin, coagulation	Every month during the first 3 mo, then every 3 mo
Reticulocytes, Alb, BUN, creatinine, immunoglobulins, autoantibodies (ANA; LKM 1), ferritin, TSH, thyroid antibodies	Every 3–6 mo
Quantitative HCV-RNA	4, 8, 12 wk, then every 3 mo
HOMA index	End of treatment

Alb = albumin; ALT = alanine aminotransferase; ANA = anti-nuclear antibody; AP = alkaline phosphatase; AST = aspartate aminotransferase; BMI = body mass index; BUN = blood urea nitrogen;  $\gamma$ -GT = gamma-glutamyl transferase; HCV = hepatitis C virus; HOMA = homeostasis model assessment; LKM = liver kidney microsomal antigen; TSH = thyroid-stimulating hormone.

annually to document SVR. Growth and pubertal development should be assessed every 6 months and bone age should be assessed at the end of treatment. Other tests may be necessary depending on the safety profile of each test drug.

## CONCLUSIONS

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.

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