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Treatment of chronic hepatitis C in children: Is it necessary and, if so, in whom?

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Hepatitis C virus (HCV) infection continues to be an important global health problem. It is estimated that approximately 170 million people worldwide are infected with HCV [1], and although children are only a small portion of those infected and the incidence of new infections has decreased in recent years, HCV still contributes to chronic liver disease in childhood [2].

Currently, transmission occurs mainly during pregnancy or at delivery, and the transmission rate is low unless the mother is HIV-coinfected. Pre-natal screening, where done, allows identification of infected mothers and early detection of the infection in their children. Current guidelines recommend testing for HCV-RNA after 18 months of age (the results being unreliable earlier in life) [3,4].

What is the natural history of hepatitis C in childhood? Several studies have tried to answer this question, but a low numbers of children in the majority of them, and the involvement in some studies of patients referred to tertiary care centres have made the results of many of these investigations questionable. Although only a very long-term prospective study on numerically valid, unselected cohorts of children infected during pregnancy or at delivery, can provide a proper estimate of the relative proportion of children who progress to end stage liver disease, studies thus far have clearly shown that children tend to have a much more benign HCV infection course than adults [5]. It is also clear that the development of severe liver disease can be accelerated by the co-occurrence of thalassemia [6], iron overload [6,7], chemotherapy [8–11], and HIV co-infection [12].

In adults, HCV therapeutic strategies have evolved from monotherapy with interferon (IFN) alfa to combination therapy with IFN alfa and ribavirin (RBV); while in children, because of RBV-associated adverse effects (i.e. reversible hemolytic anemia, fetal abnormalities and fetal death in animal studies), therapeutic strategies were initially restricted to IFN monotherapy [4,13]. In recent years, favourable results with the combination of pegylated (PEG) interferon alfa-2b and RBV have been reported in children [14,15], and the US Food and Drug Administration (FDA) has recently approved such combination therapy for use in previously untreated children with chronic hepatitis C aged 3 years or older. This approval has been based on the results of the study reported in this issue of the *Journal of Hepatology* [16]. In this multicentre (22 centres in 9 European or American countries), open-label study, Wirth et al. have evaluated the efficacy and safety of PEG-IFN-alfa-2b (60 μg/m^2/week) plus RBV (15 mg/kg/day) in 107 previously untreated children (3–17 years of age) with chronic hepatitis C and compensated liver disease [16]. Diagnosis of chronic hepatitis C was based on the presence of serum anti-HCV antibodies and HCV-RNA for more than 6 months before treatment, and histological signs of fibrosis or inflammatory activity. Children, with persistently elevated alanine aminotransferase (ALT) within 1 year before the screening, were also included in the trial.

The authors do not mention how the infection was acquired. Based on previous experiences [14,15], patients with genotype 2 or 3 with a low viral load (HCV-RNA less than 600,000 IU/ml) were treated for 24 weeks, whereas children infected with genotype 1 or 4, and genotype 3 with a high viral load (HCV-RNA greater than 600,000 IU/ml) received 48 weeks of therapy. The primary endpoint was a sustained virological response (SVR), defined as the absence of serum HCV-RNA after 24 weeks from therapy; secondary end-points were rapid virological response (RVR), defined as undetectable HCV-RNA at week 4 of treatment, and early virological response (EVR), defined as complete absence of serum HCV-RNA at week 12 of therapy. Short-term biochemical outcomes were measured in terms of normalization of serum ALT levels, whereas histological improvement was not assessed because a liver biopsy was performed only at diagnosis. The results showed a high SVR of approximately 90% in children with genotype 2 or 3, whereas in those with genotype 1 it went down to 53%. As expected, in the genotype 1 cohort RVR and EVR strongly predicted SVR, and patients with a low viral load showed a greater SVR than those with high viral load. Twelve percent of

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Abbreviations: HCV, hepatitis C virus; IFN, interferon; RBV, ribavirin; PEG-IFN, pegylated interferon; FDA, Food and Drug Administration; ALT, alanine aminotransferase; SVR, sustained virological response; RVR, rapid virological response; EVR, early virological response; US, ultrasound; ELF, Enhanced Liver Fibrosis; TE, transient elastography.

relapses were observed only in genotype 1 infected children. At the end of treatment, 77% of patients with elevated levels of ALT at baseline (approximately 47% of total patients) displayed ALT level normalization, which was associated, in the 79%, of cases with SVR.

Although during therapy all patients showed at least one adverse event, these side effects mostly fell in the mild or moderate class. However, a number of cases (28%) of psychiatric side effects (e.g. anxiety, depression, irritability, insomnia) were observed, even though antidepressant supportive therapy was not necessary; 25% of patients required dose reduction of PEG-IFN-alfa-2b or RBV for anemia, neutropenia, and weight loss, but only in one patient therapy was discontinued prematurely. Importantly, during the treatment course, weight loss and growth inhibition were common in children. Although children who experienced weight loss showed a partial, compensatory catch-up-growth after the completion of treatment, the evaluation of impact and eventual recovery of growth inhibition clearly requires a long-term follow-up. Interestingly, although a high SVR (at least 50%) was observed in all age groups between 3 and 17 years, the results show that adolescents (12–17 years) respond better to combination therapy and have fewer side effects compared to children (3–11 years). However, despite these data, the use of combined treatment is advisable, as soon as possible in children over the age of 3 with a diagnosis of chronic hepatitis C [4]. Early treatment is also recommendable to improve the quality of life that appears to be reduced in children with chronic hepatitis C with respect to healthy subjects [17]. Nevertheless, because the long-term effects of PEG-IFN-alfa-2b plus RBV are still unknown, it is currently impossible to determine whether in spite of the adverse events, combined therapy may improve the quality of life of the patient especially complete virus eradication is achieved. In addition, a more detailed study would be needed to determine how schooling affects compliance to the tolerability to treatment.

Some limitations of the study include the open label design, the small sample size (in spite of the involvement of so many centres worldwide), and the lack of a further liver biopsy performed at least 2 years after completion of treatment. A plausible alternative to liver biopsy might be the use of abdominal ultrasound (US) for evaluating steatosis in combination with non-invasive tests assessing the presence and eventually the improvement of fibrosis. As in recent years the use of serum biomarkers of fibrosis, such as ELF (Enhanced Liver Fibrosis) panel, and transient elastography (TE) have been proven very useful in detecting liver fibrosis in paediatric non-alcoholic fatty liver disease [18,19], these non-invasive techniques could also be efficiently applied to evaluate the fibrosis at the beginning and end of treatment with PEG-IFN-alfa-2b plus RBV in children with chronic hepatitis C.

Another trial has evaluated, with remarkably similar results, the use of RBV and of the other available PEG-IFN preparation. In the PEDS-C trial, published in abstract form, 114 children, with an average age of 10 years (range 5–18), were randomized to PEG-IFN-alfa-2b (180 μg per 1.73 m squared once a week) plus RBV (15 mg/kg of body weight daily), or PEG-IFN-alfa-2a alone [20]. The children were treated for 48 weeks and followed for up to 76 weeks. The proportion of children who had a sustained virological response was: 53% for those getting the combination, and 21% for those on monotherapy. Children with HCV genotype 1 had a response rate of 47% if treated with the combination and 17% if treated with monotherapy, while the comparable figures for other genotypes were 80% and 36% [20].

This well planned trial suggests a new standard in the therapeutic opportunity to treat children with chronic hepatitis C that is both efficient and rather safe, and that also represents a novel possible treatment algorithm for these children (Fig. 1). However, the question arises as whether to this date the treatment of all children with HCV infection is cost effective. It is probably not, given the low rate of progression to cirrhosis and the high cost of the drugs that makes them impossible to use in those very

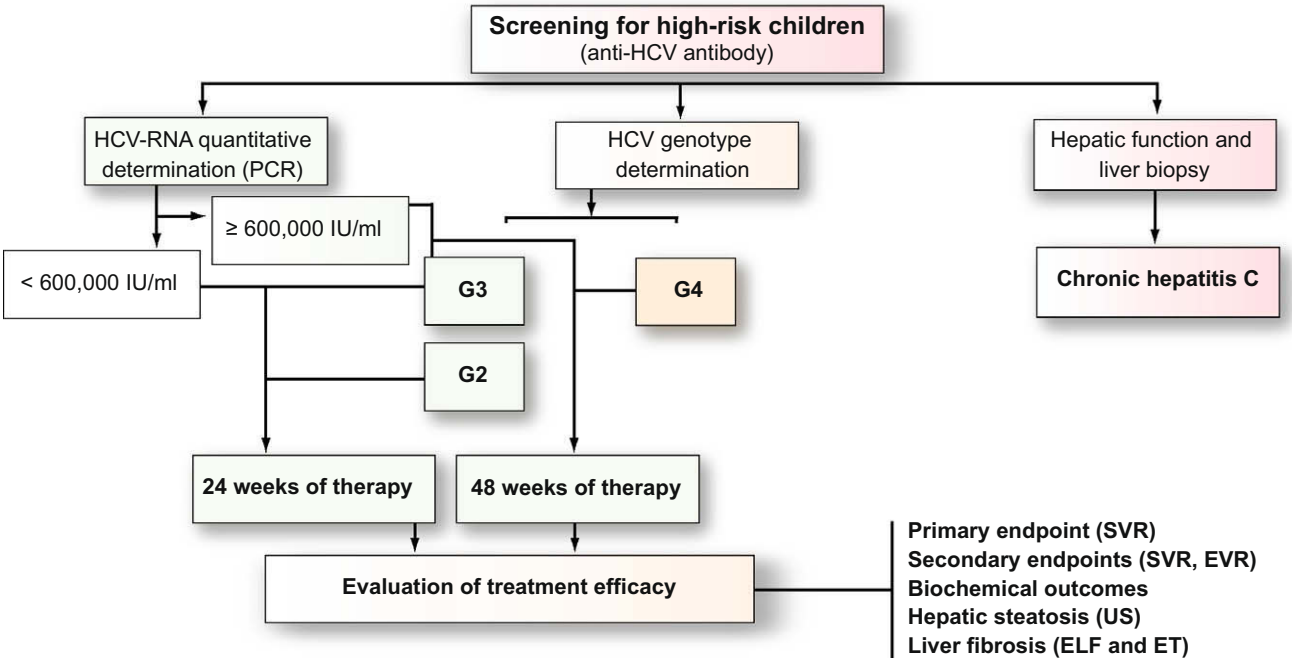

Fig. 1. Possible treatment algorithm for combined therapy PEG-IFN-alfa-2b plus RBV in children with chronic hepatitis C.

Editorial

countries (e.g., Pakistan) where HCV infection is the highest. For the time being, it would therefore be advisable to limit the treatment to those children where risk factors for severe liver disease have been identified [6–12].

Conflicts of interest

The authors declare that they have no conflicts of interest.

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