Hepatitis C virus (HCV) infection is the most common cause of chronic liver disease in the western world (1). A survey of the Third National Health and Nutrition Examination Study has shown that, between 1988 and 1994, about 18% of the American population (four million people) were HCV-positive. Despite extensive epidemiological data in adults, the exact number of children infected is still unknown, and little is known about the natural history of chronic HCV infection in childhood. The authors review studies focusing on HCV infection in children, and summarize the results, including the efficacy of interferon, and interferon plus ribavirin combination treatment of HCV hepatitis in childhood.

**Key Words:** Childhood liver disease; Children; Hepatitis C virus; Interferon; Ribavirin

TREATMENT WITH INTERFERON ALPHA

At present, interferon alpha (IFN-α) is the only product licensed for the treatment of HCV infection. Treatment aims are to achieve normalization of the liver function tests (ie, biochemical response) and loss of HCV RNA (ie, virological response) both at the end of treatment (ie, end of treatment response [ETR]) and persistently thereafter (ie, sustained response [SR]).

Since 1991, more than 80 adult clinical trials have been published focusing on IFN treatment of chronic HCV infection and, among these, 17 randomized, placebo controlled studies have been included in a meta-analysis by Poynard et al (4). This analysis showed that, after six months of 3 MU IFN-α three times per week (TIW), ETR is around 45%, while SR is only 15% to 20%. However, among those who achieved an SR, most patients remained in remission long term.

A multivariate analysis later showed that a nontransfusional source of HCV infection, low serum HCV RNA levels and liver damage through antiviral treatment is, therefore, very attractive.
and HCV genotype non-1 (eg, genotype 2a or 3a) are independent factors associated with SR to IFN therapy (5). On the other hand, persistence of HCV RNA at week 12 of treatment appears to be a predictor of no response and thus an indication to cease treatment (6).

Little is known about the efficacy of IFN in the treatment of HCV hepatitis in childhood. Details of the few published series are summarized in Table 1, and their results are outlined in Table 2. Ruiz-Moreno et al (7) reported their experience with 12 children treated with IFN for six months in an uncontrolled study. Although the results were promising (Table 2), the lack of randomization and the inclusion of HCV RNA-positive/anti-HCV-negative children raise doubts about the homogeneity and immunocompetence of the patients studied.

More recently, two small randomized, controlled clinical trials from Italy have assessed the efficacy of IFN therapy in children with HCV hepatitis without underlying medical conditions (8,9). At entry, all children in both studies had raised transaminase levels for more than six months and had histological evidence of chronic hepatitis on liver biopsy. Five children in the series of Bortolotti et al (9), however, were HCV RNA-negative. Although the treatment schedule was different in the two studies – Bortolotti et al (9) used 5 MU/m² TIW and Iorio et al used 3 MU/m² TIW – the outcomes were similar (Table 2). In the control group, only one patient in each series achieved a biochemical but not virological SR. Interestingly, all treated patients irrespective of responsiveness to IFN showed a significant improvement of liver histology (8).

The rates of SR in these two studies (43% and 45%), much higher than the 15% to 20% reported in adults, prompted the conclusion that children chronically infected with HCV respond better than adults to IFN. This observation, however, was not confirmed in a further report from one of the two centres in which the original pilot study was performed (10). Thus, in 1998, Pensati et al (10) reported a disappointing 8% virological SR in 25 children treated with IFN (Table 1). In all of these studies, the small size sample did not allow determination of SR predictors.

In children, IFN therapy is generally well tolerated, with transient influenza-like symptoms and mild hair loss being the most common side effects. Neutropenia led to a dose reduction in 45% of the children in Iorio et al’s series and in 14% in Bortolotti et al’s, while two children had to discontinue treatment (one because of a febrile convulsion and the other because of the appearance of liver kidney microsomal type 1 autoantibody concomitantly with a transaminase flare).

**COMBINATION TREATMENT WITH IFN AND RIBAVIRIN**

Ribavirin is a synthetic guanosine nucleoside homologue. In vitro, it has activity against RNA and DNA viruses. It has been used in pilot studies and in trials of adults with chronic...
HCV infection. As monotherapy, it improves liver function tests and histological features but has no antiviral effect (11-13).

Results of two large multicentre, randomized, placebo controlled trials of combination therapy with IFN and ribavirin in over 1700 treatment-naive adult patients were recently published (14,15). Patients were randomly assigned to receive 24 or 48 weeks of IFN plus ribavirin or IFN alone. These studies showed that combination therapy is significantly better than monotherapy in terms of virological, histological and biochemical improvement 24 weeks after cessation of treatment (Table 3). The combination therapy was effective in all types of patients, including those with high viral load, advanced fibrosis and genotype 1 infection. Combination therapy was generally well tolerated, but dosage modification and discontinuation of treatment were more frequent than with IFN monotherapy, although side effects were those previously observed with IFN alone or ribavirin alone with no synergy. Adverse effects specific to ribavirin include dose-dependent reversible hemolytic anemia, cough, pruritus, rash and insomnia.

When ribavirin was given with IFN, hemolysis was the main reason for dose reduction. The mean maximum hemoglobin decrease from baseline was observed at four weeks of therapy and remained relatively constant thereafter. After stopping the medication the hemoglobin returned to baseline values.

In pediatrics, ribavirin use is approved for respiratory syncytial virus infection and has been safely used in children for human immunodeficiency virus (16) and for severe measles infection (17). A multicentre, phase I, randomized, open-label, multiple-dose, uncontrolled study is in process to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of ribavirin plus IFN in pediatric patients with chronic HCV. This study aims to indicate the dose of ribavirin to be used and will give some information on the efficacy and safety of this combination therapy in childhood.

Although the introduction of the IFN plus ribavirin combination therapy has considerably improved the response rate, at least in adults, more efficient drugs and/or treatment schedules are continuously sought. IFN high dose induction (18-20) and daily dosing (21-23) have shown encouraging results in adult studies. For pediatric patients, it is particularly important to improve not only the efficacy, but also the tolerability of the treatment. Slow-release INF, such as PEGylated IFN (PEG IFN) (21), are particularly attractive. PEG IFN was developed to decrease systemic clearance of IFN-2a and thereby prolong the exposure to this drug, potentially improving the clinical outcome while decreasing the dosing frequency. Pharmacodynamic studies have shown that PEGylation of IFN resulted in a slower absorption rate, decreased systemic clearance and prolonged serum half-life, providing much more sustained trough levels than standard IFN following a single subcutaneous injection (24). Thus, a single weekly dose would be sufficient to maintain therapeutic serum levels of IFN. There is no doubt that this approach would be more tolerable and would increase compliance, particularly in children.

FUTURE WORK

While ribavirin plus IFN combination therapy, high dose induction or daily IFN, and PEG IFN are being tested, the molecular virology and pathogenesis of HCV infection are being intensively investigated. Identification of essential virally encoded enzymes will provide the rationale to focus research efforts at the discovery of their specific inhibitors. The enzymes under intense study are the HCV protease, helicase and RNA-dependent RNA polymerase. Molecular engineered new drugs targeting these specific virally encoded functions will soon be available for trials.

REFERENCES
