Treatment of pediatric hepatitis C : results and perspectives

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Interferon-alfa (IFN) seems to be the only therapy of proven benefit in the treatment of adult patients with chronic hepatitis C (CHC).

However, in the last few years, the enthusiasm for this therapy has been tempered by the observation that only a small percentage (15-25%) of the treated patients have a long-term beneficial response. On the basis of this observation, predictive factors of a sustained beneficial response have been researched in order to treat only those whose likelihood of a response warrants the expense and discomforts of the 6-12 months of therapy (1). A favourable response to IFN has been associated with pre-treatment factors such as : low HCV-RNA serum levels, viral genotype 2 or 3, low levels of genetic diversity of HCV, absence of fibrosis or cirrhosis on liver biopsy (1).

As far as IFN therapy in children with CHC is concerned, pediatric patients seem to have an asymptomatic disease characterised by an isolated hypertransaminasemia with mild-moderate liver damage and with a good prognosis in the short-term. On the basis of these features, it is debated if children with CHC have to be considered for IFN treatment. On the other hand, it is well known that in adulthood CHC is the principal cause of cirrhosis and hepatocellular carcinoma and is a frequent indication for liver transplantation. In order to avoid the progression of disease, children with CHC have been treated with IFN. The first pediatric studies reported encouraging response rates, but the lack of standardised terminology for description of response has made the comparative evaluation of the response rates very difficult.

The first pediatric study was a pilot uncontrolled study by Ruitz-Moreno *et al.* (2). In this study only 3 (25%) out of 12 patients showed a biochemical and virological response at the 18th month of post-therapy follow up. It is to note that in this study all the enrolled patients were HCV-RNA positive, but only 5 of them were anti-HCV positive. This serological pattern is not typical of immunocompetent children so that the results of this study must be interpreted with caution.

Subsequently, two randomised controlled studies, regarding children with CHC and without other chronic systemic diseases, have been published (3,4). Although in both studies the number of the enrolled patients was very small, the results were quite interesting.

In an Italian multicenter study the percentage of biochemical and virological responders were very high (78% and 71%, respectively) at the end of IFN treatment (12th month) and almost satisfactory at the 12th month of posttherapy follow-up (55% had biochemical response and 78% virological response) (3).

In another study, performed at our Department, 45% of the treated patients showed both biochemical and virological response at the end of therapy (12th month) and none of them showed either biochemical or virological relapses during a 12-month course of post-therapy follow-up (4).

It is to note that the lack of relapse in our study was probably related to a more careful definition of response to therapy. In fact, in our study patients were considered responders when ALT normalisation and HCV-RNA negativation occurred during the treatment and persisted for the entire period of observation. In other words, both biochemical and virological response were not evaluated only at the end of therapy and at the end of follow-up but on many occasions.

In these studies an improvement in liver histology following IFN therapy was also observed. In particular, in our study the evaluation of follow-up biopsies performed in the group of treated patients showed a significant improvement in total Knodell's score, periportal necrosis and portal inflammation in responders compared to nonresponders (4).

Little information is available about the long-term response rates in children with CHC, as well as about viraemic changes during IFN treatment. Recently, at our Department of Pediatrics we have studied the behaviour of serum HCV-RNA before and during IFN therapy in order to better define the response to therapy in children with CHC.

A long-term response (both virological and biochemical) was observed in only 8% of 25 children treated with recombinant-alfa2b IFN (5 MU/m^2 t.i.w.) for 12 months and followed up for other 12 months after IFN discontinuation.

It is to note that during the entire period we have observed that about 40% of patients showed phases of normalisation of ALT and/or of negativation of serum HCV-RNA, but we have considered responders only the patients with persistent normalisation of ALT and persistent negativation of serum HCV-RNA.

As previously reported, the sustained responders, observed in our study, had low basal levels of viremia and genotypes other than Ib. Also in our experience, responders showed a very early viral clearance associated with ALT normalisation, usually within the first month of therapy.

Therefore, considering the small percentage of responders and the high costs of IFN therapy (in terms of direct medical costs and of deterioration of health-related quality of life), at the present time it is desirable to treat only children with basal factors known to be associated with a favourable response to IFN. This recommendation derives from pediatric studies performed on a small number of patients (3,4), but is also supported by larger studies concerning adult patients (1).

Furthermore, we think that when a child is enrolled to IFN therapy, in absence of positive predictive factors, a 2-month course of IFN is sufficient to understand it a favourable response may be achieved : it there is no response within 2 months, IFN should be stopped.

As for new approaches to therapy of CHC, promising results have been achieved with ribavirin in combination with IFN alfa in adults (1). So far, in pediatric age this therapeutic approach has not been utilised.

References

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