Interferon - alpha treatment for chronic hepatitis C in children

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Interferon-alpha therapy has been proven efficient in chronic hepatitis C infection. Although it has been used as a standard therapy in adults, there are limited data on benefits of interferon treatment in children.

We conducted a study of recombinant interferon-alpha therapy in 10 children with chronic hepatitis C. They had high aminotransferase values and positive antibodies to hepatitis C virus and HCV-RNA for at leas six months. Interferon-alpha was given at a dosage of 5 million units/m^2 body surface three times a week for six months. At the end of therapy, five (50%) of the patients had complete response and two partial response. Three patients were nonresponders. Eight of the patients could be followed up for six months after stopping therapy, at which point one of the four complete responders and a partial responder relapsed. One of the three nonresponders had complete response at 12 months. Eventually, four (50%) of eight patients were complete responders. All of the nonresponders were the patients with previous malignant diseases.

These findings suggest that interferon-alpha has beneficial effects in children with chronic hepatitis C, and a six month therapy seems to be reasonable. Patients with underlying malignant disease are not good candidates for interferon treatment.

Key words: interferon, chronic hepatitis C, children.

Chronic hepatitis C is typically an insidous and slowly progressive disease. In some patients, cirrhosis and even hepatocellular carcinoma develop. It affects all age groups, but is uncomon in children[1-4]. Clinical studies have indicated that chronic hepatitis C has a poor propensity to spontaneous remission[5], and treatment is necessary with antiviral drugs.

Recently, interferon (IFN) -alpha has been used as the main medical treatment for patints with chronic hepatitis C and has been shown to be effective in decreasing the level of hepatocellular injury and inflammation and the risk of hepatocellular carcinoma[6,7]. Large randomized studies have reported the efficacy of IFN with 50 percent response rate, though the rate of relapse following IFN withdrawal is still high[7-14].

Reports about IFN-alpha treatment for chronic hepatitis C in children are rare. Here we report our experience with the use of IFN-alpha in 10 children with chronic hepatitis C virus infection.

Material and Methods

Ten children (7 boys, 3 girls) with chronic hepatitis C, aged between five and 16 years (median 8 years) were eligible for this study. Five had been treated for different types of malignancies (ganglioneuroma, ganglioneuroblastoma, Hodgkin's lymphoma, Burkitt's lymphoma and medulloblastoma) and one had sickle cell anemia. Patients were included if they had persistently elevated serum aminotransferase activities and positive HCV-RNA for the last six months before enrollment. Criteria for exclusion were antiviral or immunosuppressive therapy during the preceeding 12 months, leukopenia (< $3X10^9$/L), thrombocytopenia (< $100X10^9$/L), elevated serum creatinine level, other causes of liver disease, presence of HBsAg in serum, clinical and biochemical evidence of autoimmunity and decompensated liver disease.

Liver disease caused by alpha-1-antitrypsin deficiency and Wilson's disease was ruled out by the usual diagnostic means. At entry, patients were tested for antinuclear antibody, anti-smooth muscle antibody, anti-DNA thyroid functions, and cryoglobulinemia.

Serum samples were tested for qualitative detection of antibody to hepatitis C virus (anti-HCV) by a microparticle enzyme immunoassay

(MEIA) test (Abbott-AxSYM, HCV Version 3, USA). The kits were based on four viral antigens (HCr 43, c200, c100, NS5). HCV-RNA was copied into cDNA by reverse transcription and amplified by the nested polymerase chain reaction (PCR) using primers for the 5'-non-coding region of HCV at entry and at three-month intervals. Genotypes of HCV-RNA were determined using restriction fragment length polymorphism of the PCR product generated from the 5'-untranslated end of the genome, and genotypes were classified according to the nomenclature proposed by Simmonds et al.[15]. Liver biopsy was performed on all patients within six months before start of IFN-alpha therapy. Family members were screened for the presence of anti-HCV in serum.

Interferon-alpha treatment was initiated no sooner than three years after treatment of the underlying disease had been completed in those patients with malignancy. A written informed consent was obtained from the parents.

After evaluation, patients were started on IFN-alpha 2b (Intron-A, Schering-Plough CO. Country Cork, Ireland) subcutaneously at a dose of 5 million units/m^2 three times per week for six months. Eight patients were followed for six months after the end of treatment. Two had just finished the therapy.

Patients were evaluated monthly with liver function tests and hematological parameters during the treatment and then at three-month intervals for the following six months. An abnormal serum alanine aminotransferase (ALT) value was defined as 50 IU/L or greater.

A complete response was defined as serum ALT within normal ranges, and undetectable HCV-RNA at the end of therapy. Partial response was identified as normal ALT values or undetectable HCV-RNA. Nonresponders were those with persistently high ALT levels and positive HCV-RNA. Relapse was defined as recurrence of elevated ALT with reappearance of HCV-RNA in serum during the follow-up period.

Results

The study group consisted of 10 patients with a mean duration of hepatitis C of 11 months (range, 6-24 months). The source of hepatitis was presumed to be from blood transfusions in six and unknown in four patients. None of the family members had anti-HCV in the serum. All children were symptom free and none had a history of acute or chronic liver disease. Patients with previous malignancies had been off chemotherapy for three to 12 years (median 5 years). All had normal physical findings; serum ALT levels fluctuated between 65 and 401 IU/L. There was no evidence of autoimmunity, cryoglobulinemia or thyroid disorders in any patient.

Table I summarizes the clinical and laboratory data. Anti-HCV and HCV-RNA were positive in the serum of all 10 patients before treatment. HCV genotyping studies showed that seven patients had HCV genotype Ib, and three had genotype Ia. Liver biopsy revealed chronic persistent hepatitis in seven and mild hepatitis in the remaining three patients.

Table I. Laboratory Data in Patients Treated with Interferon-alfa 2b During Therapy and Through the Follow-up Period

		ALT (IU/L)				HCV-RNA		
Patient	Genotype	at Entry	3 mo	6 mo*	12 mo	3 mo	6 mo*	12 mo
1	Ia	65	53	12	18	+	–	–
2	Ib	231	70	40	30	–	–	–
3	Ib	175	15	15	25	+	–	–
4	Ia	151	45	17	73	+	–	+
5	Ib	89	39	34	NI	+	–	NI
6	Ia	247	130	88	68	–	–	+
7	Ib	198	70	71	NI	+	–	NI
8	Ib	85	75	69	82	+	+	+
9	Ib	197	85	69	31	+	+	–
10	Ib	232	85	86	85	+	+	+

ALT: Alanine aminotransferase (normal < 50 IU/L).
NI : Not identified.
* : End of treatment.

At the end of six months of IFN-alpha therapy, HCV-RNA became undetectable in seven patients (70%), and five of these had normal serum ALT levels. Therefore, five (50%) of the patients had complete response with normal ALT and undetectable HCV-RNA. Two were partial responders with high serum ALT and negative HCV-RNA. Three children were nonresponders. all three nonresponders and one partial responder were patients with previous malignant diseases. At the third month of treatment only two children had negative HCV-RNA Eight patients (4 complete and 1 partial responder, 3 nonresponders) were followed for six months after the end of treatment. One of the patients with complete response relapsed (patient 4); six months later HCV-RNA was detected and ALT values increased. One of the three nonresponders (patient 9) eventually cleared the virus and became a complete

responder with negative HCV-RNA and normal ALT at 12 months. The patient showing partial response became HCV-RNA positive six months after stopping the treatment. Thus, at 12 months, four of eight patients (50%) had complete response. Two nonresponders never cleared HCV-RNA and had persistently abnormal ALT. All four nonresponders were patients with underlying malignant diseae. Two nonresponders had genotype Ib and two had Ia; three respondes had HCV genotype Ib.

Every child had fever and malaise after the first doses of IFN-alpha, but no serious side effects were observed.

Discussion

The natural history and treatment of chronic hepatitis C has not been well documented in children. It seems that the disease in children usually follows an asymptomatic course and that severe liver disease is uncommon during childhood, presumably because of the slow rate of progression[10,16]. More severe disease may be expected with increasing age, and spontaneous resolution of HCV is rare. Fujisawa et al.[5] reported spontaneous remission in only 8.3 percent of children with chronic hepatitis C. Thus the treatment of chronic hepatitis C in children should be considered.

The most common modes of HCV transmission are blood transfusion and vertical transmission from mothers infected by HCV[1]. Five patients with different types of malignant diseases and one with sickle cell anemia had histories of blood transfusion. None of the mothers or other family members had anti-HCV in their sera. Thus, four of the patients (40%) had unknown etiology of HCV infection. Approximately 35-50 percent of patients with anti-HCV have been reported to have none of the risk factors for HCV infection[17,18]. Because children with malignant diseases may be immunocompromised because of the primary disease itself or of the cytotoxic agents used for treatment, IFN therapy was started at least three years after the end of treatment of primary disease.

In general, younger age, short duration of the disease, absence of cirrhosis, and mild histology have been considered as positive predictive factors for IFN treatment of chronic hepatitis C[19,20]. None of our patients had cirrhosis on the histological examinatilon, predicting response to IFN treatment. Genotype viral load also predicts the results of IFN therapy[21]. Children are at a prolonged risk for sequelae, such as cirrhosis and hepatocellular carcinoma. As they have most of the positive predictive factors naturally, children with chronic hepatitis C seem to be ideal candidates for IFN treatment. The goal of treatment in children should be to clear the virus and prevent progression to severe liver diseases. In addition to its ability to prevent the progression of liver disease, IFN is also of benefit in patients with hepatitis C virus infection who respond to this treatment, by lowering their risk of developing hepatocellular carcinoma[7,22].

In adults, IFN-alpha has been shown to induce sustained biochemical and virological response with amelioration of histological findings[23]. Little information is available about IFN treatment in children[9,14]. Complete response rate has been reported as 33-56 percent in these studies, depending on the definition of response and duration of treatment. Geographic differences may be important in response to IFN treatment, possibily due to viral genotype or host factors. In our study, 50 percent of patients had complete response at the end of six months of IFN-alpha treatment. Although two of the patients had just finished the therapy, complete response rate was the same at 12 months. An interesting point was that one child, who was a nonresponder at the end of therapy, became a complete responder at 12 months without additional therapy, similar to the report of Jonas et al.[14]. This finding may be due to spontaneous clearance of HCV. In fact, termination of IFN therapy, has been suggested for patients with positive HCV-RNA at three months of therapy[14,23]. In our study, only two of the five complete responders had negative HCV-RNA at three months of therapy. Two of seven patients (28.5%) with undetectable HCV-RNA at six months relapsed at 12 months. Jonas et al.[14] also suggested continuation of IFN treatment if the patients showed complete response at six months in order to decrease the relapse rate. Complete response rate was 33.8 percent with 12 months of therapy in their study. Although our patients were treated for only six months, complete response rate was almost similar to that in adults (50%), and the relapse rate was lower. In fact, our follow-up period was not adequate to ensure that the patients will not have a later relapse. All nonresponders at 12 months were the patients with malignant diseases. Cesaro et al.[24]

had also indicated that patients cured of a pediatric malignancy are not good candidates for IFN therapy for hepatitis C.

Recent investigators have shown that the HIV genotype was one of the important factors in predicting response to IFN therapy[19]. In most series, genotype Ib has been shown to be associated with higher HCV-RNA levels, more severe hepatitis, and a higher frequency of decompensated cirrhosis, and patients infected with HIV genotype Ia or Ib show poor response to IFN treatment[9,19,25,26]. Although seven of our patients had HCV genotype Ib and three had genotype Ia, complete response rate of IFN treatment in our patients was higher than that in these studies. Nonresponders had both HCV genotype Ia and Ib.

IFN has a variety of side effects, some of which cause dose decrease or discontinuation of the therapy. In this study, IFN-alpha was generally well tolerated, and only an influenza-like syndrome was seen during the first doses of IFN.

This study showed that IFN-alpha was safe and had beneficial effects in children with chronic hepatitis C, but it is not hopeful in patients with underlying malignant disease. A combination of ribavirin and IFN may be effective in cases unresponsive to IFN therapy[27]. Ongoing HCV-RNA positivity at the third month did not imply nonresponse in our three patients. As termination of therapy for nonresponders at the third month does not seem to be reasonable, we suggest at least six months of therapy, even if HCV-RNA persists at the third month. In fact, further long-term studies with larger numbers of patients are needed to show the real efficacy of IFN treatment in children with chronic hepatitis C.

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