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TREATMENT OF CHRONIC NON-A,NON-B HEPATITIS WITH RECOMBINANT HUMAN ALPHA INTERFERON

A Preliminary Report

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Abstract We treated 10 patients who had chronic non-A,non-B hepatitis with recombinant human alpha interferon in varying doses (0.5 to 5 million units) daily, every other day, or three times weekly for up to 12 months.

In 8 of the 10 patients, elevated serum aminotransferase levels decreased rapidly during therapy and eventually fell into the normal or nearly normal range. In two of these patients, the interferon therapy was stopped after four months, and in both cases, a prompt return of aminotransferase activities to pretreatment values occurred. Prolonged treatment was associated with a sustained improvement in aminotransferase levels; in three cases, biopsy specimens obtained after one year of therapy showed marked improvement in hepatic histology, even though low doses of alpha interferon had been used.

These preliminary findings, although not adequately controlled, suggest that long-term, low-dose alpha interferon therapy may be effective in controlling the disease activity in some patients with chronic non-A,non-B hepatitis. A prospective controlled trial is now needed to assess the role of interferon therapy in this disease. (N Engl J Med 1986; 315:1575-8.)

NON-A,NON-B hepatitis is a common and important cause of liver disease and cirrhosis. It is the leading cause of post-transfusion hepatitis, and it accounts for 20 to 40 percent of cases of sporadic hepatitis.[1-5] Non-A,non-B hepatitis has a marked propensity to progress to chronic liver disease. In as many as 60 to 70 percent of cases of post-transfusion non-A,non-B hepatitis, the patients continue to have elevations in serum aminotransferase levels for more than a year.[2-4] Although many cases of chronic non-A,non-B hepatitis are asymptomatic and mild, an estimated 15 to 25 percent lead to considerable liver injury, with an insidious progression to cirrhosis, portal hypertension, and hepatic failure.[1,6-8] There is currently no effective therapy for chronic non-A,non-B hepatitis; corticosteroids do not appear to be beneficial.[1]

The recent availability of highly purified and potent preparations of recombinant human alpha interferon has allowed trials of this antiviral and immunomodulatory agent in the treatment of several acute and chronic viral illnesses. Alpha interferon has been reported to have beneficial effects in chronic type B hepatitis and delta hepatitis.[9-13] We report here the results of a preliminary study of 10 patients with chronic non-A,non-B hepatitis who received prolonged therapy with recombinant human alpha interferon.

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METHODS

Patients

Ten patients who fulfilled the criteria for the diagnosis of non-A,non-B hepatitis were treated with alpha interferon. All patients had chronic fatigue, persistent elevations in serum aminotransferase levels, and liver-biopsy changes indicative of chronic hepatitis. All had a history of possible exposure to non-A,non-B hepatitis; hepatitis had developed in six of the patients after blood transfusions, in three after parenteral drug abuse, and in one during employment in northern Africa. None had alcoholism or other obvious disorders that could have caused liver disease.

The 10 patients (9 men and 1 woman) were white and ranged in age from 26 to 62 years old (mean, 40). They had had elevations in serum alanine and aspartate aminotransferase levels for more than a year (mean, 6.4 years; range, 1.4 to 19.5). Furthermore, their serum aminotransferase levels had been consistently higher than 2.5 times the upper limit of the normal range on multiple occasions (mean, 8 determinations; range, 5 to 12) during the previous year. Serum direct bilirubin levels were normal in all the patients; the serum albumin level was low in one, and the prothrombin time was prolonged in another. All the patients had normal serum levels of ceruloplasmin, copper, iron, transferrin, and alpha-1-antitrypsin. All were negative for antinuclear and mitochondrial antibodies; seven had smooth-muscle antibody, and one had rheumatoid factor. Serum samples from all 10 were negative for hepatitis B surface antigen and hepatitis B virus DNA on multiple occasions. One patient had stable levels of antibodies to hepatitis B surface and core antigens. Liver biopsies performed within eight months of the

beginning of treatment showed chronic persistent hepatitis in one patient, chronic active hepatitis in six, and chronic active hepatitis with cirrhosis in three.

Interferon Therapy

Treatment consisted of subcutaneous injections of recombinant human alpha interferon (Alfa-2b, Intron, kindly provided by the Schering Corporation, Kenilworth, N.J.). The patients were taught how to give the injections to themselves; thus, after the first week, all therapy was administered outside the hospital. In the first seven patients, the initial dose of interferon was 5 million units (MU) daily. The other three patients started with a lower dose of 1 MU daily. In all subjects, the dose was gradually decreased on the basis of changes in serum aminotransferase activity and the presence of side effects. After the dose was reduced to 1 MU daily, the dosage schedule was changed so that the interferon was given either on alternate days or three times per week (Monday, Wednesday, and Friday). To date, three patients have been treated for 12 months and the remainder for 2, 3, 4, 5, 5, 9, and 10 months, respectively. Follow-up liver biopsy specimens were obtained in the three patients who were treated for 12 months. All patients gave written informed consent to participate in the study, and all details of the protocol were approved by the Clinical Research Subcommittee of the National Institute of Diabetes and Digestive and Kidney Diseases.

Results

Alpha interferon therapy was associated with a marked and sustained decrease in serum aminotransferase levels in 8 of the 10 patients treated (Table 1). The decreases in serum levels of the aminotransferases began within one to four weeks of the start of treatment and were usually sustained for as long as the interferon therapy was continued. In six patients, the serum aminotransferase levels fell into the normal range and subsequently remained normal, despite a reduction in the dose of alpha interferon to 1 MU three times weekly. These six patients are still receiving interferon. In two other patients, the serum aminotransferase levels decreased markedly but remained mildly elevated (less than 1.5 times the upper limit of the normal range); these patients have received interferon intermittently. In the remaining two patients, serum aminotransferase activities did not decrease, and interferon was stopped after two and four months.

Table 1. Serum Aminotransferase Levels in 10 Patients with Chronic Non-A,Non-B Hepatitis Treated with Recombinant Human Alpha Interferon.*

Patient No.	Duration of Therapy	Current Dose of Interferon	Alanine Aminotransferase		Aspartate Aminotransferase	
			At Start	At End	At Start	At End
	mo	*million units†*	*U/liter*		*U/liter*	
1	12‡	None	219	62	90	53
2	4§	None	416	273	282	251
3	12	1	376	24	167	27
4	12	1	200	25	157	27
5	10	3	148	44	125	46
6	2§	None	392	358	161	193
7	9	1	460	34	153	23
8	5	1	306	38	121	29
9	5	1	272	24	122	26
10	3	1	185	29	85	23
Mean			297	91	146	70

*The normal values are below 45 U per liter for alanine aminotransferase and below 31 U per liter for aspartate aminotransferase.

†All patients listed received the dose of interferon shown three times a week, except for Patient 5, who was treated daily.

‡Interferon therapy was stopped in this patient after 12 months of treatment.

§Interferon therapy was stopped in these patients because of apparent lack of effect.

The course of the first patient who was treated with alpha interferon is shown in Figure 1. Initially, the patient had an active cirrhosis, with serum aminotransferase levels that were persistently elevated for more than nine years. The aminotransferase levels began to decrease within one week of the start of alpha interferon therapy and remained only minimally elevated for the entire period of therapy, despite a reduction in the dose to 0.5 MU daily. After a year of treatment, the interferon was stopped, and the serum aminotransferase levels remained low during the subsequent 12 months of follow-up evaluation.

Therapy was discontinued after only four months in two patients whose serum aminotransferase levels became normal while they were receiving alpha interferon (Fig. 2). In both patients, the serum aminotransferase levels returned to pretreatment values within one to two months after discontinuation of therapy. Reinstitution of interferon therapy at a lower dose was followed by another decrease in serum aminotransferases into the normal range; the pattern of the response was similar to that observed during the first course of treatment. On the basis of these results, we decided to continue interferon therapy for at least 12 months in all patients whose serum aminotransferase activities improved during the treatment.

The three patients whose courses are shown in Figures 1 and 2 underwent a follow-up liver biopsy one year after they began to receive alpha interferon. In all three cases, the post-treatment liver-biopsy specimens showed a marked improvement in the degree of portal inflammation and a disappearance of parenchymal hepatocytic necrosis. In one case, the biopsy findings indicated a change from an active cirrhosis to an inactive cirrhosis; in the remaining two, the change was from chronic active hepatitis to chronic persistent hepatitis or to minimal, nonspecific changes.

The principal side effects of the interferon therapy were fatigue, achiness, headaches, irritability, and fever. These side effects were common with a dose of 5 MU daily. The side effects decreased when the dose of interferon was lowered. At a dose of 1 MU three times a week, most patients had no appreciable side effects.

Discussion

Research into non-A,non-B hepatitis has been frustrated by the failure to identify an agent associated

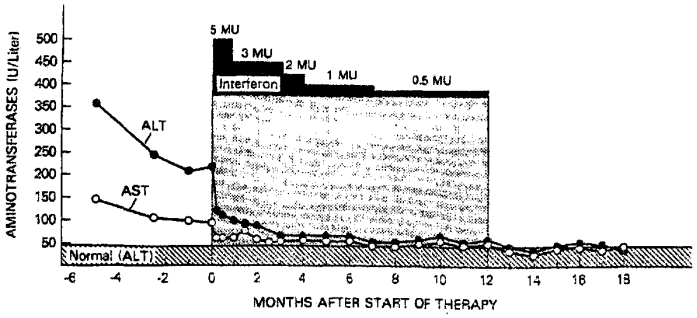

Figure 1. Serial Determinations of Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST) Levels in a Patient (No. 1) with Chronic Non-A,Non-B Hepatitis Who Was Treated for One Year with Daily Injections of Recombinant Human Alpha Interferon.

The doses of interferon were 5, 3, 2, 1, and 0.5 million units (MU) per day, as indicated above the stippled area.

with this disease.[14-16] Non-A,non-B hepatitis is clearly a transmissible disease, but the agent that causes it has not been isolated, and reliable serologic markers for the infection have not yet been developed. Because of these problems, measurement of serum aminotransferase activities has been the only convenient means of detecting and monitoring non-A,non-B hepatitis.[2,3,16]

Alpha interferon was a natural choice as a possible therapeutic agent for chronic non-A,non-B hepatitis. This agent has a wide spectrum of antiviral activity and has been used to treat many acute and chronic viral illnesses. Alpha interferon has already been shown to inhibit replication of several human hepatitis viruses, including hepatitis A virus (in cell cultures),[17] hepatitis B virus,[9-12] and the hepatitis delta agent.[13]

In this study, initiation of interferon treatment was followed by prompt and marked decreases in serum aminotransferase activities in 8 of 10 patients with well-documented chronic non-A,non-B hepatitis. The speed with which the decreases in aminotransferase levels occurred after the initiation of alpha interferon therapy and the reproducibility of these responses during retreatment provided strong evidence that the interferon had an effect on the disease and that the changes observed were not coincidental. The rapid improvement in the results of serum biochemical liver tests in patients with chronic non-A,non-B hepatitis is in contrast to the delayed beneficial effects of alpha interferon in patients with chronic hepatitis B.[10,11] The rapid improvement we observed suggests that hepatocellular injury in chronic non-A, non-B hepatitis is a direct result of viral replication and is less dependent on immunologically mediated injury, which appears to be the cause of liver damage in chronic hepatitis B.

The decrease in serum aminotransferase activities in our patients with chronic non-A,non-B hepatitis was usually sustained for as long as the interferon was continued, even when the agent was given in low doses. Whether this improvement will be sustained after discontinuation of treatment remains to be shown. In one patient in this study, the improvement was sustained after interferon therapy was stopped after a year of treatment. In two other patients, however, stopping the interferon therapy after only four months of treatment was followed by a prompt increase in aminotransferase levels to pretreatment values. These findings suggest that prolonged therapy with alpha interferon will be needed to obtain a sustained beneficial effect in non-A,non-B hepatitis. The use of low doses given three times weekly makes such prolonged therapy practical.

The reproducibility of the decreases in aminotransferase levels in patients with non-A,non-B hepatitis given alpha interferon treatment was striking. However, the natural course of chronic non-A,non-B hepatitis often includes wide, spontaneous fluctuations in serum aminotransferase activities.[1,15] For this reason,

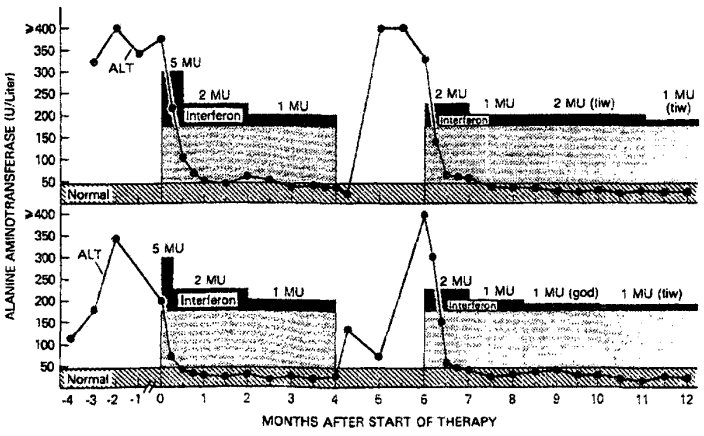

Figure 2. Serial Determinations of Alanine Aminotransferase (ALT) Levels in Two Patients (No. 3 and 4) with Chronic Non-A,Non-B Hepatitis Who Were Treated with Two Courses of Recombinant Human Alpha Interferon.

The doses of alpha interferon, 1 to 5 million units (MU) daily, every other day (qod), or three times weekly (tiw), are indicated above the stippled areas.

the association of the decreases in serum enzyme activities with the initiation of alpha interferon therapy needs to be confirmed by prospective, randomized, and controlled trials. Furthermore, the importance of the changes we observed in aminotransferase levels in relation to the underlying liver histology, as well as to the ultimate course and outcome of the disease, requires further study. Non-A,non-B hepatitis remains a disease that is difficult to diagnose and that has an uncertain natural history.[1,15,16] The encouraging results of this preliminary study indicate the need for a prospective assessment of the possible role of long-term, low-dose interferon in the treatment of this chronic viral illness.

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