[原著] Predicting factors and efficacy of interferon alpha therapy in patients with liver cirrhosis associated with HCV infection

Predicting factors and efficacy of interferon alpha therapy in patients with liver cirrhosis associated with HCV infection

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ABSTRACT

The present study examined the efficacy and the predicting factors of response to interferon (IFN) alpha in patients with liver cirrhosis associated with hepatitis type C virus infection (LC type C). Sixty-seven patients were treated with IFN alpha and were classified into 2 Groups. Group 1 : Patients with liver cirrhosis, showing histological liver cirrhosis or chronic active hepatitis with lobular disorganization. Group 2 : Patients with chronic hepatitis, showing histological chronic persistent hepatitis or chronic active hepatitis without lobular disorganization. Sustained response to IFN was obtained in 5/17 (29.4%) and 24/50 (48%) of patients in Group 1 and Group 2, respectively. However, the difference was not significant. All patients in Group 2 showed a significant decrease in alanine aminotransferase (ALT) levels during the treatment, whereas 5 of the 17 patients in Group 1 showed no response. All sustained responders in Group 1 who were tested for serum HCV-RNA titer showed low serum HCV-RNA titer, which was less than 10^7 copies/ml, while all except one patient of the non-responders of Group 1 showed above 10^8 copies/ml. It is said that patients with LC type C are more resistant to IFN treatment compared to those with chronic hepatitis type C. However, our findings suggest that even in patients with LC type C, low serum HCV-RNA levels might be associated with better response to IFN. *Ryukyu Med. J., 16(3)117~121, 1996*

Key words: interferon alpha, liver cirrhosis, hepatitis type C

INTRODUCTION

Hepatitis type C virus (HCV) infection accounts for more than 70% of liver cirrhosis in Japan, and patients with liver cirrhosis associated with HCV are said to have a high risk of hepatocellular carcinoma (HCC)[1]. Moreover, the mortality rate of HCC associated with HCV has been increasing in Japan, and even if the patients with HCV infection do not develop HCC, they are expected to develop complications of liver cirrhosis (such as ascites, esophageal varices). Treating HCV related liver cirrhosis may contribute to not only decrease the mortality rate of HCC patients but also reduce the complications of liver cirrhosis. Therefore, the management of patients with LC type C is an important clinical issue in Japan. Interferon (IFN) therapy is currently the only effective antiviral agent for the treatment of chronic hepatitis type C. However, there have been few reports which examine the efficacy of IFN in patients with liver cirrhosis as it has been thought that IFN treatment is ineffective and can cause deterioration in these patients. The present study evaluated the efficacy of IFN treatment and the predicting factors of response to the treatment in LC type C patients.

PATIENTS AND METHODS

From April, 1992 to March, 1994, a total of 67 patients with chronic hepatitis or liver cirrhosis type C were treated with IFN alpha in our institutes. Patients were 42 males and 25 females with a mean age of 54.1±9.1 years. The patients were positive for anti-HCV by second generation enzyme immunoassay. The patients were classified into two groups. Group 1 : Seventeen patients with liver cirrhosis, showing histological liver cirrhosis or chronic active hepatitis with lobular disorganization (CAH + LD). There were 9 males and 8 females with a mean age of 54.3±9.3 years, and 8 of the 17 (47.1%) patients had received blood transfusion. The mean duration from blood transfusion to initiation of IFN treatment was 24.6 years. On the other hand, Group 2 comprised 50 patients with chronic hepatitis,

Table 1 Background factors before treatment

	No. of cases	Gender (M/F)	Average age (yr)	BT (%)	Duration from BT (yr)
Group 1	17	9/8	54.5± 9.3	47.1	24.6
Group 2	50	33/17	47.9±12.8	62.0	11.5
Total	67	42/25	54.1± 9.1	58.2	14.2

Group 1 : Liver biopsy showed liver cirrhosis or CAH + lobular disorganization
Group 2 : Liver biopsy showed CAH without LC or lobular disorganization
Abbreviation : BT, blood tranfusion

Table 2 Treatment regimens of IFN

Type and dose of IFN	Treatment duration			
	13 weeks course		24 weeks course	
	Group 1 (n=1)	Group 2 (n=11)	Group 1 (n=16)	Group 2 (n=39)
IFN α-2a 900MU[1]	1	9	6	16
IFN α-2a 600MU[2]	0	1	4	5
IFN α-2b 600MU[3]	0	1	6	18

[1] IFN α-2a 900 MU : every day for 2 weeks + 3 times/week for 11 or 22 weeks
[2] IFN α-2a 900 MU : every day for 2 weeks + IFN α-2a 600 MU : 3 times/week for 11 or 22 weeks
[3] IFN α-2b 600 MU : every day for 2 weeks + 3 times/week for 11 or 22 weeks
Abbreviation : MU, million units

showing histologically mild to moderate activity without liver cirrhosis or lobular disorganization. There were 33 males and 17 females with a mean age of 47.9±12.8 years. Thirty-one of the 50 (62.0%) patients had a history of blood transfusion. The mean duration of HCV infection was 11.5 years (Table 1).

Pretreatment serum HCV-RNA titer was quantified by multi-cyclic reverse transcription polymerase chain reaction (PCR) method. And HCV genotyping was carried out by PCR using type-specific primers as described by Okamoto et al[2].

Treatment regimens are shown in Table 2. All patients were administered recombinant interferon alpha for 13 to 24 weeks, with a total dose of 282-720 million units (MU). The regimens were not significantly different between Group 1 and Group 2. All patients were followed up for more than 6 months after completion of the therapy.

The response pattern of IFN alpha therapy can be divided into 4 groups: (1) Sustained response (SR): Alanine aminotransferase (ALT) returned to the normal range during the treatment and remained at the normal value for more than 6 months after completion of the treatment; (2) Relapse (Re): ALT returned to the normal range during the treatment but rose above the normal range after cessation of the treatment; (3) Breakthrough (Br): ALT appeared to decrease in the early phase of the IFN treatment but increased again despite continuation of the treatment; (4) No response (NR): There was no significant decrease of ALT levels during or after the treatment (Fig.1).

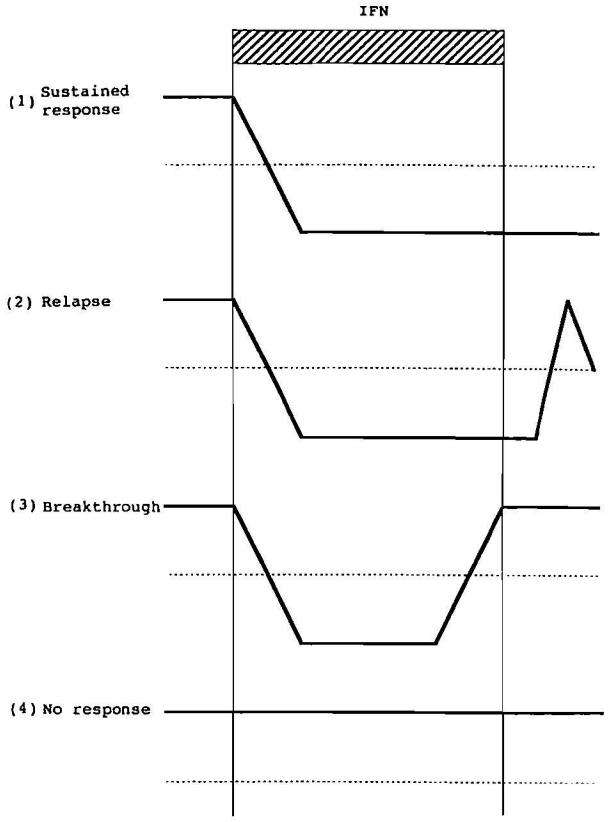

Fig.1 Reaction patterns of ALT during IFN treatment.
———: ALT reaction pattern
.....: Normal upper limit of ALT

RESULTS

The sustained response rate of IFN treatment in Group 1 and Group 2 was 29.4% (5/17) and 48% (24/50), respectively (Table 3).

HCV-RNA of all SR patients has not been detected by multi cyclic reverse transcription polymerase chain reaction 6 months after completion of the therapy.

The clinical course of Group 1 is described in Fig.2. As seen in Table 3, there were no statistically significant differences in the rate of SR between Group 1 and Group 2. The remaining three response patterns between Group 1 and

Table 3 Response to treatment according to IFN regimens between Group 1 and Group 2

	Sustained response cases(%)	Relapse cases(%)	Breakthrough cases(%)	No response cases(%)
Group 1 (n=17)	5(29.4)	3(17.6)	4(23.5)	5(29.4)
Group 2 (n=50)	24(48)	18(36)	8(16)	0(0)

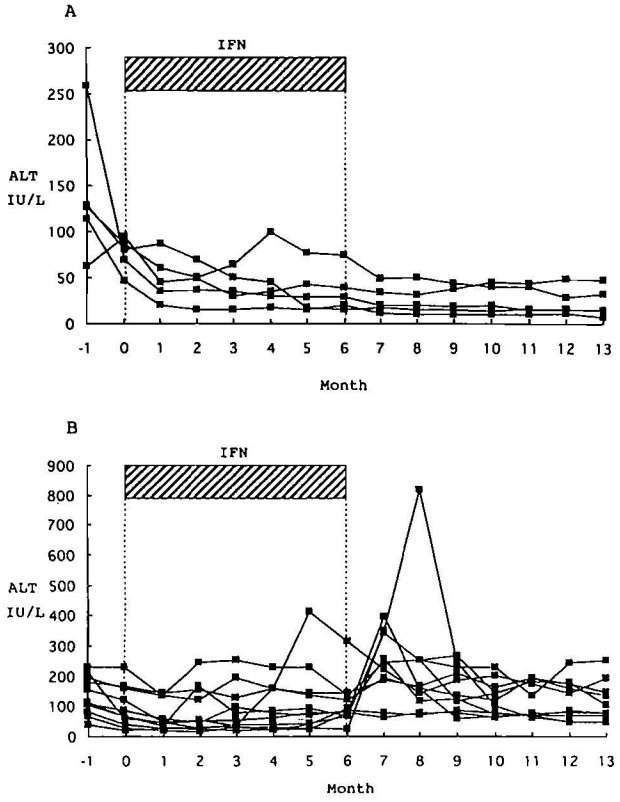

Fig.2 Clinical course of Group 1. A : Patients with sustained response (n=5). B : Patients with other than sustained response (n=12).

Group 2 were 3 and 18 patients with Re, 4 and 8 with Br, 5 and none with NR, respectively (Table 3).

HCV genotype was determined in 10 patients in Group 1. Genotype II were seen in 8 patients, including 2 patients with SR and another 2 patients had genotype III. The two patients infected with HCV genotype III consisted of one patient in SR and another in Br (Table 4).

Serum HCV-RNA titer was quantified in 11 of the 17 patients in Group 1. In the 5 patients showing SR in Group 1, 4 were measured for serum HCV-RNA. All four patients showed serum HCV-RNA titer of less than 10^7 copies/ml. On the other hand, 7 of 12 patients who showed other than SR in Group 1 were quantified HCV-RNA titer. Six of the 7 were above 10^8 copies/ml, and the remaining patient showed 10^6 copies/ml (Pt. No. 10) (Table 4).

During the IFN treatment, no serious side effects were observed; however, minor side effects were seen in Group 1 and Group 2; respectively: fever (100%, 100%), muscle and joint pain (100%, 80.0%), fatigue (47.1%, 38.0%), head ache (52.9%, 56.0%), appetite loss (52.9%, 62.0%), leukopenia (41.2%, 46.0%), thrombocytopenia (23.5%, 26.0%). The frequencies of these side effects did not differ between Group 1 patients and Group 2 patients.

Table 4 Relation of HCV-Genotype, and HCV-RNA level with response pattern of ALT in Group 1

	HCV-Genotype	HCV-RNA level(copies/ml)	Reaction pattern of ALT
1)	II	10^7	Sustained response
2)	II	10^6	〃
3)	—	10^2	〃
4)	III	10^2	〃
5)	—	—	〃
6)	II	10^9	Relapse
7)	II	10^9	〃
8)	—	—	〃
9)	II	10^{10}	Breakthrough
10)	III	10^6	〃
11)	—	—	〃
12)	—	—	〃
13)	II	10^9	No response
14)	II	10^8	〃
15)	II	10^9	〃
16)	—	—	〃
17)	—	—	〃

DISCUSSION

Interferon alpha was first reported to have beneficial effects on chronic hepatitis C in 1989 by Hoofnagele et al[3]. Since that time, IFN has been the only useful therapy for the treatment of patients with chronic hepatitis C (CH-C). Interferon alpha induces 2',5'-oligoadenylate synthetase (2-5AS), proteinkinase (PKase), 2'-phosphodiesterase. These enzymes show antiviral effects; 2-5AS breaks down viral RNA[4], PKase and 2'-phosphodiesterase inhibits the production of viral protein[5]. Therefore, most patients with CH-C treated with IFN alpha have a normalization of serum ALT during the therapy. However, biochemical and virological relapse are frequently seen after completion of the therapy. The sustained response rate of IFN in CH-C is reported to be only around 30%[6]. Furthermore, CH-C is a steadily progressive course leading to the development of liver cirrhosis, and is frequently accompanied by hepatocellular carcinoma (HCC). Hence, it is important to treat the liver cirrhosis, which has the high risk of developing into HCC[7]. However, there have been few

reports that examined the efficacy of IFN treatment in LC type C. Patients with cirrhosis, leukopenia and thrombocytopenia are often observed as hypersplenism. Therefore, the administration of IFN can cause problems by reducing the number of leukocytes (neutrophils in particular) and platelets. The administration of IFN sometimes induces a rise in transaminase levels, which aggravates liver injury. In view of such problems, it has often been considered difficult to use IFN treatment for patients with cirrhosis.

Recently, in an attempt to develop a new therapeutic strategy to reduce relapses and cure CH-C, steroid priming on IFN has been evaluated. But this treatment has only a marginal benefit over treatment with IFN alone[8]. Furthermore, it is said that in patients with liver cirrhosis type B, steroid withdrawal therapy frequently induces acute exacerbation, which sometimes results in hepatic insufficiency[9]. Hence, steroid priming therapy was not standard procedure for patients with LC type C. So we evaluated the efficacy and predicting factors in patients with LC type C by using IFN alone.

The sustained response rate of IFN in Group 1 was 29.4%, the rate being comparable to that in Group 2. There were no differences between the Groups. Furthermore, Saito et al. reported that sustained response to IFN treatment was seen in 40% of patients with compensated LC type C[10]. These findings suggest that pathological features did not affect the response to IFN therapy.

It has been reported that IFN is more effective in patients infected with genotype Ⅲ or Ⅳ than in those with genotype Ⅱ[11]. In the present study, 10 patients who were assessed for genotype in Group 1. Sustained response was seen in 2 of 8 (25%) of patients with genotype Ⅱ, and in one of the two patients with genotype Ⅲ. Since the number of patients who had been examined for HCV-genotype was very small, we could not discuss the association of HCV-genotype with the effectiveness of IFN.

Previous reports have shown that low pretreatment serum HCV RNA titer contributed to better therapeutic outcome in patients with chronic hepatitis C[12~14]. In our study, all patients with sustained response to IFN treatment in Group 1 showed pretreatment serum HCV-RNA titer of less than 10^7 copies/ml. On the other hand, none of the patients with a pretreatment HCV-RNA level being greater than 10^8 copies/ml in Group 1 showed sustained response to the treatment. This indicates that HCV RNA level is a very important predicting factor for response to IFN treatment in LC type C.

In our study, successful IFN treatment produced an increase of peripheral platelet counts in some of the patients with liver cirrhosis (data not shown). This finding suggests that successful IFN treatment might lead to improvement of hypersplenism caused by hepatic circulation disorders.

However, it remains unknown whether successful IFN treatment contributes to the reduction of the risk of HCC. A long-term study is needed to evaluate the effect of IFN treatment on the development of HCC.

In conclusion, there was no significant difference in sustained response rate between Group 1 patients and Group 2 patients. Even in patients with LC type C, low serum HCV-RNA level might be associated with better response to IFN alpha treatment and sustained response to IFN in such patients might improve the condition of liver cirrhosis.

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