

# Clinical study on the treatment of liver fibrosis due to hepatitis B by IFN- $\alpha_1$ and traditional medicine preparation \*

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**Subject headings** hepatitis B; liver cirrhosis/therapy; interferon- $\alpha$ ; drugs, Chinese herbal

## INTRODUCTION

In China, liver fibrosis in most patients resulted from the viruses of hepatitis B. Both anti-virus and anti-fibrosis should be considered in designing a program for the treatment of liver fibrosis. Therefore, 40 cases of liver fibrosis due to hepatitis B were treated by using IFN- $\alpha_1$  and traditional medicinal preparations from February 1994 to April 1996. Good curative effect was achieved.

## MATERIALS AND METHODS

### *Clinical materials*

A group of 40 patients (33 men and 7 women) was investigated. Their age ranged from 28 years to 45 years with a mean of 36. Their course of disease was from 4 years to 12 years, averaging 7 years. All patients had the typical history of hepatitis B. The diagnosis of liver fibrosis was confirmed by experimental serology and liver biopsy (the criteria of diagnosis referred to the criteria amended during the 5th National Academic Conference on Infectious Diseases and Parasitic Diseases). Patients whose clinical manifestations were not consistent with the findings in serological and pathohistological tests were not included in the study.

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\*Supported by the key project of the "8th Five Year Plan" of Scientific Committee of Guizhou Province (1993 No. 2037) and the key project of the "9th Five Year Plan" of Scientific Committee of Guizhou Province. (1996 No.1028)

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Received 1997-12-02 Revised 1999-01-18

### *Therapeutic*

All the patients received intramuscular injection of 3 000 000U IFN- $\alpha_1$  (Produced by Shengzhen Kexing Company, batch number 94010), once a day for the first month, and once two days after a month. Traditional medicinal preparation (composed mainly of Tetrandrae, Salvia miltiorrhiza Bge, Semen Ginkgo, Radix paeoniae rubrae, each gram has 0.8 g herb, produced by Duyun Pharmaceutical Factory, Guizhou Province, batch number 940102) was taken, three times a day for 3 months (45 g/d). Besides vitamin E and C, none of other medicines had been used in this group.

### *Observation index and methods*

Detection of serum liver fibrosis indexes and hepatitis B virus marker: 6 mL serum was taken from the patients before treatment, by the end of treatment and 6 months after treatment respectively. Laminin (LN), hyaluronic acid (HA) and procollagen type III (PC III) were measured by radioimmunoassay (the reagents were purchased from Shanghai Naval Medical Research Institute and Chongqing Tumor Research Institute). Radioimmunoassay was also used to detect the markers of hepatitis B virus such as HBsAg, anti-HBs, HBeAg, anti-HBe, HBcAg and anti-HBc. HBV-DNA was measured by PCR (the reagent was bought from 3V Company, Shandong Province).

### *Ultrasonography and fibergastroscopy*

Each patient was detected once by HPSONOS-1000 Colour Doppler (HP Company of USA) before and after the treatment and by direct vision fibergastroscopy (Olympus-XQ20, Japan).

### *Liver biopsy*

The liver tissue was quickly taken by fine needle under local anesthesia. The liver tissue was about 3 cm long. It was fixed by 10% formalin, then imbedded in paraffin, sliced and routinely stained. These slices taken from 12 biopsied patients before and after the treatment were read by single blind method. After a pathologist read these slices according to the criteria, another pathologist reported the results after reread them.

**Table 1 Comparison of the 5 serum indexes of the 40 patients before and after treatment and after 6 months of follow-up ( $\bar{x} \pm s$ )**

Time	n	LN	PCIII	HA	Albumin	Globulin
		(ng/L)	(ng/L)	(ng/L)	(g/L)	(g/L)
Before treatment	40	420.0 $\pm$ 68.0	146.2 $\pm$ 44.8	182.40 $\pm$ 42.20	30.51 $\pm$ 2.42	26.25 $\pm$ 6.84
After treatment	40	290.3 $\pm$ 36.4 <sup>b</sup>	112.4 $\pm$ 30.6 <sup>b</sup>	136.32 $\pm$ 39.20 <sup>b</sup>	35.25 $\pm$ 4.46 <sup>b</sup>	31.32 $\pm$ 6.74 <sup>b</sup>
Effective type after 6 months follow-up	22	142.6 $\pm$ 32.8 <sup>c</sup>	80.0 $\pm$ 31.8 <sup>c</sup>	84.54 $\pm$ 36.33 <sup>c</sup>	39.13 $\pm$ 3.24 <sup>c</sup>	25.98 $\pm$ 3.22 <sup>c</sup>
Non-effective type after 6 months follow-up	18	403.5 $\pm$ 41.5 <sup>a</sup>	156.3 $\pm$ 43.9 <sup>a</sup>	178.20 $\pm$ 38.60 <sup>a</sup>	29.35 $\pm$ 2.71 <sup>a</sup>	37.00 $\pm$ 4.54 <sup>a</sup>

<sup>a</sup> $P < 0.05$ ; <sup>b</sup> $P < 0.001$ , compared with those before treatment; <sup>c</sup> $P < 0.001$  the effective type compared with the non-effective type.

## RESULTS

The serum LN, HA, PC III and globulin of the 40 cases after treatment were noticeably lower than those before treatment ( $P < 0.001$ ). The albumin was obviously increased compared with that before treatment ( $P < 0.001$ ). After 6 months of follow-up, LN, HA and globulin in the effective type (HBsAg, HBeAg and HBV-D NA turned negative after using IFN $\alpha_1$ , suggesting that the viruses of hepatitis B were temporarily suppressed. Otherwise, it was considered to be non-effective type) were obviously lower than those in the non-effective type ( $P < 0.001$ ), while the albumin was obviously higher than that in the non-effective type ( $P < 0.001$ , Table 1).

Before treatment, 32 patients were found with HBsAg, anti-HBc and HBeAg; 8 patients with HBsAg and anti-HBc; and 21 patients with HBV-DNA. After 3 months of treatment, HBsAg, HBeAg and HBV-DNA became negative in 6 (15%), 16 (50%), and 16 (76.2%) patients, respectively. Among the 12 patients who received liver puncture biopsy, dekris-type necrosis disappeared in 3 patients, no obvious proliferation of fiber with more new-born liver cells in one patient, improvement of bridge-joint necrosis with elimination of the ramus septi-fibrosis in 3 patients, improvement of bridge-joint with new-born liver cells and unclear ramus septi-fibrosis in 2 patients, complete foliole with a great number of liver cells in 3 patients. Before treatment, the portal vein of 34 patients was  $\geq 14$  mm in width among the 40 patients, while after treatment, the portal vein of 28 patients was  $\leq 12$  mm. After 6 months of follow-up, among the 28 patients, the portal vein of 23 patients was  $\leq 11$  mm, the others remained 12 mm. Before treatment, the blood flow rate of portal vein in 36 patients was  $\geq 16$  mm/s, while after treatment, it was  $\leq 12$  mm/s in 32 patients. No change was found in the rest. By using fibergastroscopy the line or snake-shaped grey-white or grey-blue changes could be seen at the lower segment of esophageal mycoderma in 32 patients before treatment, while the changes disappeared in 28 patients after treatment. No obvious changes were found in 4 patients.

## DISCUSSION

Up to now, there has been no good way to cure liver fibrosis resulting from chronic hepatitis B. A number of researches have been made by domestic scientists who had made great progress by using traditional medicines such as *Salvia miltiorrhiza* Bge, *Tetrandrae*, *Radix paeoniae rubrae* and *Prunus persicae* (L), batsch *et al*<sup>[1-3]</sup>. However these methods have not been considered to suppress the virus of hepatitis B. For this reason, some tests were made by using IFN $\alpha_1$  and traditional medicinal preparations to treat 16 patients with early-stage hepatic cirrhosis, and have achieved rather good curative effect which was confirmed by liver biopsy before and after treatment<sup>[4]</sup>. On the other hand, short-term curative effect was significant in 20 patients treated simply by the traditional medicinal preparations<sup>[5]</sup>, but there was recurrence in some patients. Therefore, IFN $\alpha_1$  and traditional medicinal preparation were used to treat hepatitis and liver fibrosis at the same time. At present IFN $\alpha_1$  is regarded as one of the most effective agents to treat hepatitis B because it is a biologically regulatory and active material with antiviral and immunoregulatory function<sup>[6,7]</sup>. *Tetrandrine* is an effective ingredient of *Tetrandrae*. In modern medicine the research has proved that it can block the channel of calcium on the cytomembrane of liver, obstruct the depletion of ATP in the cytomembrane, protect the liver cells, and inhibit the proliferation of internal lipocyte of liver and synthesis of collagen. The effective ingredients of dansheng are *Tanshinone* and *tanshine* which may suppress the reaction of inflammation and promote the regeneration of liver cells by reducing the degeneration and necrosis of liver cells. The effective ingredient of chichao is *paeoniflorin* which may improve the microcirculation of liver, decrease the portal pressure and promote the histologic change of liver fiber. Flavonoid substance in ginkgo leaves can strengthen the immunologic function of body, decrease the free radical of oxygen, increase the activity of NK cells and intensify the anti virus capacity of body<sup>[8,9]</sup>. After 3 months of treatment with the herbal medicinal preparations, the changes of LN, HA, PC III, albumin and globulin were

obviously different from those before treatment, which were confirmed by liver biopsy, ultrasonography and fibergast roscopy. It is suggested that this preparation can improve the function of liver and suppress the fibrosis of liver in a short time. Follow-up was made for 6 months after withdrawing the medicine. The result proved that the difference between IFN $\alpha_1$  effective type and ineffective type was very obvious. It indicated that the virus of hepatitis B was suppressed in the patients cured by IFN $\alpha_1$ , and the liver fibrosis due to clinical hepatitis B was continuously improved or reversed by using the traditional herbal preparations which can cure liver fibrosis. The patients in this group are being followed up continuously.

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Edited by WANG Xian-Lin