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• VIRAL HEPATITIS •

Clinical observation of salvianolic acid B in treatment of liver fibrosis in chronic hepatitis B

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Abstract

AIM: **To evaluate the clinical efficacy of s*alvianolic acid* B (SA-B) on liver fibrosis in chronic hepatitis B.**

METHODS: **Sixty patients with definite diagnosis of liver fibrosis with hepatitis B were included in the trial. Interferon-g (IFN-g) was used as control drug. The patients took orally SA-B tablets or received muscular injection of IFN-g in the double blind randomized test. The complete course lasted 6 months. The histological changes of liver biopsy specimen before and after the treatment were the main evidence in evaluation, in combination with the results of contents of serum HA, LN, IV-C, P-III-P, liver ultrasound imaging, and symptoms and signs.**

RESULTS: **Reverse rate of fibrotic stage was 36.67 % in SA-B group and 30.0 % in IFN-g group. Inflammatory alleviating rate was 40.0 % in SA-B group and 36.67 % in IFN-g group. The average content of HA and IV-C was significantly lower than that before treatment. The abnormal rate also decreased remarkably. Overall analysis of 4 serological fibrotic markers showed significant improvement in SA-B group as compared with the IFN-g group. Score of liver ultrasound imaging was lower in SA-B group than in IFN-g group (HA 36.7 % *vs* 80 %, IV-C 3.3 % *vs* 23.2 %). Before the treatment, ALT AST activity and total bilirubin content of patients who had regression of fibrosis after oral administration of SA-B, were significantly lower than those of patients who had aggravation of fibrosis after oral administration of SA-B. IFN-g showed certain side effects (fever and transient decrease of leukocytes, occurrence rates were 50 % and 3.23 %), but SA-B showed no side effects.**

CONCLUSION: **SA-B could effectively reverse liver fibrosis in chronic hepatitis B. SA-B was better than IFN-g in reduction of serum HA content, overall decrease of 4 serum fibrotic markers, and decrease of ultrasound imaging score. Liver fibrosis in chronic hepatitis B with slight liver injury was more suitable to SA-B in anti-fibrotic treatment. SA-B showed no obvious side effects.**

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INTRODUCTION

Radix Salviae Miltiorrhizae (Sm) can activate blood circulation and resolve stasis and is a commonly used herb clinically[1]. Sm was applied to the late-stage schistosomial cirrhosis and splenomegaly at first time in 1958[2]. Later Dr. Yu used its injection to treat hepatitis B at the early-stage cirrhosis[3], the biopsy examination before and after treatment identified that Sm could effectively alleviate the pathological changes of liver fibrosis. *Salvianolic acid B* (SA-B), a major water soluble component in Sm[4], protected the tetrachloride carbon (CCl_4) induced fibrosis in rats, and reversed dimethylnitrosamine (DMN) induced liver fibrosis in rats. It could prevent liver cell injury, inhibit proliferation of hepatic stellate cells (HSC) and collagen production *in vitro*[5-9]. Based on the stable preparation procedures and long-term toxic test on rats, we used SA-B tablets and interferon-γ (IFN-γ) injection as control drug in the double blind randomized clinical trial[10-16]. The liver biopsy examination before and after treatment was used as a major evalulation standard, assisted by serum fibrotic markers, liver ultrasound imaging, liver function test, symptoms and dynamic observation of regular test of blood, urine, and renal function, in order to study the clinical efficacy, indications, and side effects of SA-B in liver fibrosis with chronic hepatitis B.

SUBJECTS AND METHODS

Subjects

Patients having liver fibrosis with chronic hepatitis B were included in the trial. Initially 77 patients were involved, but 17 of them were not included in the final analysis because of following reasons: 1) 4 patients showed no obvious liver fibrosis in their first liver biopsies; 2) 7 patients failed to undertake their second liver biopsies; and 3) 6 patients' liver specimen were too small to make pathological examination.

Before and after the treatment, the liver biopsy specimens of 60 patients were in accordance to pathological diagnosis 30 patients in SA-B group, 28 males and 2 females and 30 patients in IFN-g group, 28 males and 2 females. The age in SA-B group was 36.1±9 years, and in IFN-γ group 35.1±7.8 years. Duration of hepatitis B in SA-B group was 3.9±3.2 years, and 3.6±4.6 years in IFN-γ group. There was no significant difference in grade and stage of pathological examinations between two groups before treatment.

Diagnostic criteria

History: The patient had a history of hepatitis B or HBsAg carrier and still had the symptoms and signs of hepatitis and

abnormal liver function when included in the trial. Etiological marker: HBsAg was positive. Ultrasound imaging: In accordance to the ultrasound images of chronic hepatitis B. Liver biopsy examination: Definite pathological diagnosis of liver fibrosis. The fibrotic stage was S1-S4. Symptoms: Pain in the hepatic region, general fatigue, anorexia and abdominal distention. Signs: Hepatomegaly, splenomegaly, hepatica facies, palmar erythema, vascular spiders.

Criteria to enroll subjects

Age: 18-60 years, in accordance to the diagnostic criteria for liver fibrosis in hepatitis B. Histological fibrotic stage was S1-S4.

Criteria to exclude subjects

(1) Over 60, or less than 18 years of age. Patient in pregnancy or in breast feeding period. (2) Complicated with hepatitis C or other hepatic viral infection; suspicion of autoimmune hepatitis; and drug hepatitis or alcoholic hepatitis. (3) Decompensated post-hepatitic cirrhosis. (4) Severe complications of cardiovascular systems, renal, or hematopoietic system; mental diseases. (5) Failure to achieve twice liver biopsy or failure to make pathological diagnosis with liver biopsy specimens. Patients meeting any one of the above criteria were excluded from the trial.

Group and administration

Grouping The patients were divided into two groups based on their randomized number they received.

Drug The double blind randomized method was used. SA-B tablet (30 mg/tablet) and placebo tablet (made of excipient), having same package and labels, were named Gan Xian Ling I and Gan Xian Ling II respectively. All the tablets were prepared by the Shanghai Institute of Drug, Chinese Academy of Sciences. Interferon-g injection (IFN-γ, 1MU/injection) and placebo injection (made of substrate without IFN-γ activity) having the same package and labels were named IFN-γ I and IFN-γ II respectively. Injections were provided by the Shanghai Clone Biological High Technology Limited Company (Product NO.980508, revelation after treatment).

Drug administration Double blinded method was used in drug administration. The group I patients were orally administered with Gan Xian Ling I tablet, 2 tablets t.i.d for 6 months. And patient had muscular injection of IFN-γ-I once a day in the first month and then once every other day in the following five months. The group II patients were administrated with Gan Xian Ling II and IFN-γ-II. The usage was the same as in group I.

Regular items observed

Recording and observation of symptoms and signs Patient' s symptoms and signs were recorded in detail using "Clinical Observation Table" once a month before and during the treatment.

Etiological markers of hepatitis B HBV marker: ELISA, the kit was obtained from Shanghai Ke Hua Company. HBV-DNA: PCR, the kit was from Hua Mei Company (PCR-HT420III).

Liver function The patient had liver function examination (Tai Er Kang Automatic Biochemical Instrument) every month during the treatment, including contents of serum proteins, total bilirubin, direct bilirubin, and activities of ALT (Alanine Aminotransferase) and AST (Aspartate Aminotransferase). The kit was a product of Shanghai Ke Hua-Dong Ling Diagnostic Instrument Company.

Liver ultrasound imaging Specific professional technicians were assigned to do the ultrasound imaging of liver, gallbladder and spleen (HITACHIEUB-410 type) for the patients and made records. Based on the literature, rate and score each item (liver surface, liver parenchyma, liver edge, intra-hepatic vessels)[17], Table 1.

Table 1 Ultrasound image scoring for liver fibrosis

Items	1	2	3
Liver surface	Normal (smooth)	Irregular	Waved-shaped (or serrated)
Liver edge	Normal (sharp)	Blunt at tip	Blunt at the edge
Liver parenchyma	Normal (even)	Rough	Nodular(or patch-like)
Intra-hepatic vessels	Normal(clear)	Elusive	Unevenly narrow, wide,thick or thin

Serum fibrotic markers The serum from each patient was collected before, during,and after treatment and stored at-70 ℃. All the serum specimens, at one time, were examined by Shanghai Changzheng Hospital (PLA Clinical Immune Center) in a blinded manner.Hyaluronic acid (HA): radioimmunoassay, the kit was from Shanghai Navy Medical Institute. Laminin (LM): radioimmunoassay, the kit was from Shanghai Navy Medical Institute. Type IV Collagen (C-IV): ELISA, the kit was from Shanghai Seng Xiong Technology Enterprise Company. Type-III-procollagen-N-peptide (P-III-P): radioimmunoassay, the kit was from Shanghai Oren Diagnostic Instrument Limited Company.

Histopathological examincation of liver

Each patient had percutaneous liver biopsy guided by ultrasound imaging within one week before and after treatment. The liver biopsy specimens were fixed by 10 % formalin and embedded by paraffin according to the routine procedures. HE stain: sections (4 μm) were routinely HE stained. Collagen stain: double stain reticular fibers and collagen fibers by Gorden-Sweet method and Masson trichrome method.

Sections with HE stain and collagen stain and pathological diagnosis were made by three pathologists in a blinded manner, according to "1995 National Prevention and Treatment Plan of Viral Hepatitis" [18,19](inflammatory grades and fibrotic stages were determined when more than two pathologists reached the same diagnosis).

Side effects and security

Negative response of each patient was carefully observed and recorded during treatment. Each patient received EKG, renal function examination, regular blood test and regular urine test before, during and after treatment.

Images and analysis

Radit analysis was used for rank data of pathological grades and stages. *t*-test or analysis for variance was used for measurement data and χ^2 test for enumeration data.

RESULTS

Correlation between serum fibrotic markers and pathological changes of liver fibrosis

The serum fibrotic markers were generally consistent with the valuation of stages and grades (Tables 2 and 3, Figures 1 and 2). Although the standard deviation of markers (individual difference) was large, combined use of HA, P-III-P and IV-C was much better and serum LM content was in normal ranges.

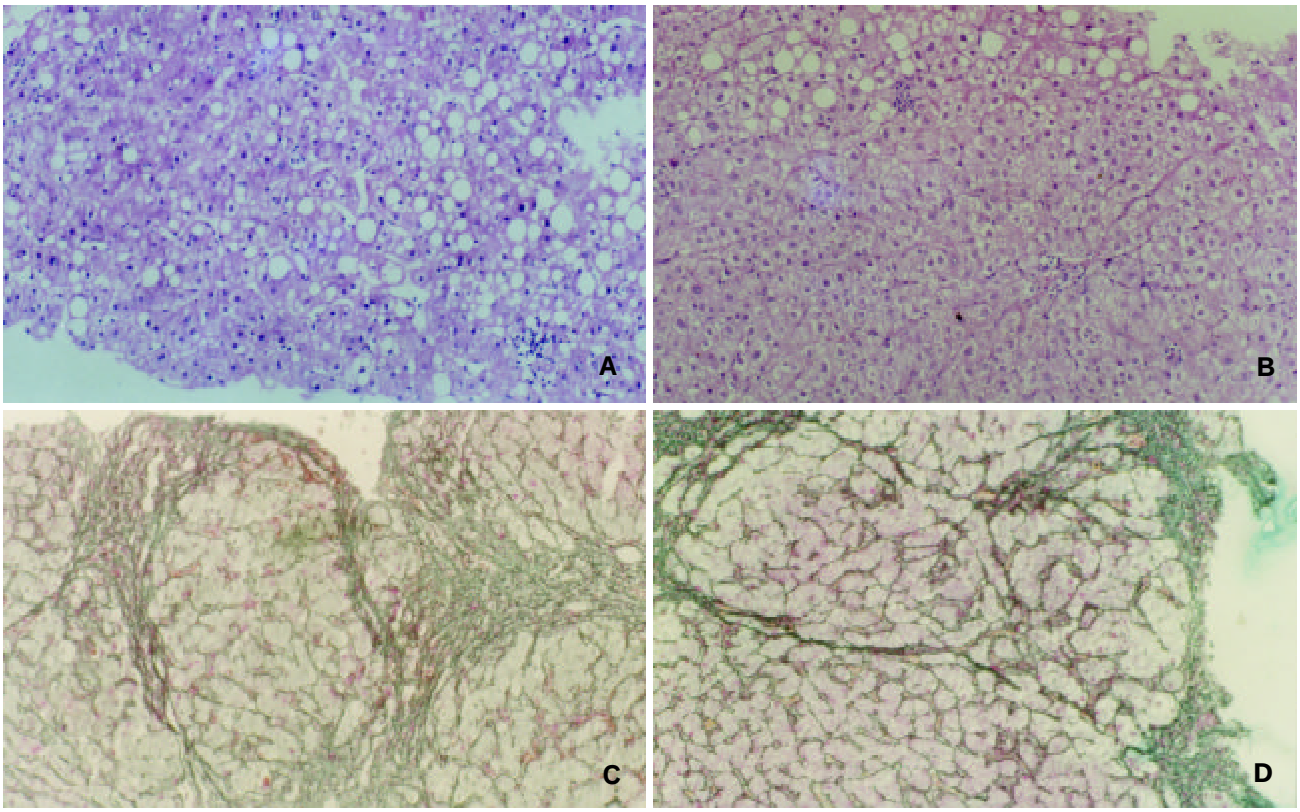

Figure 1 Histological changes of liver biopsy specimens before and after treatment in IFN-γ group:
A: First liver biopsy (G3, HE stain, ×100) before treatment; B: Second liver biopsy (G3, HE stain, ×100) after treatment;
C: First liver biopsy (S4, collagen stain,.×100) before treatment; D: Second liver biopsy (S3, GS stain, ×100) after treatment.

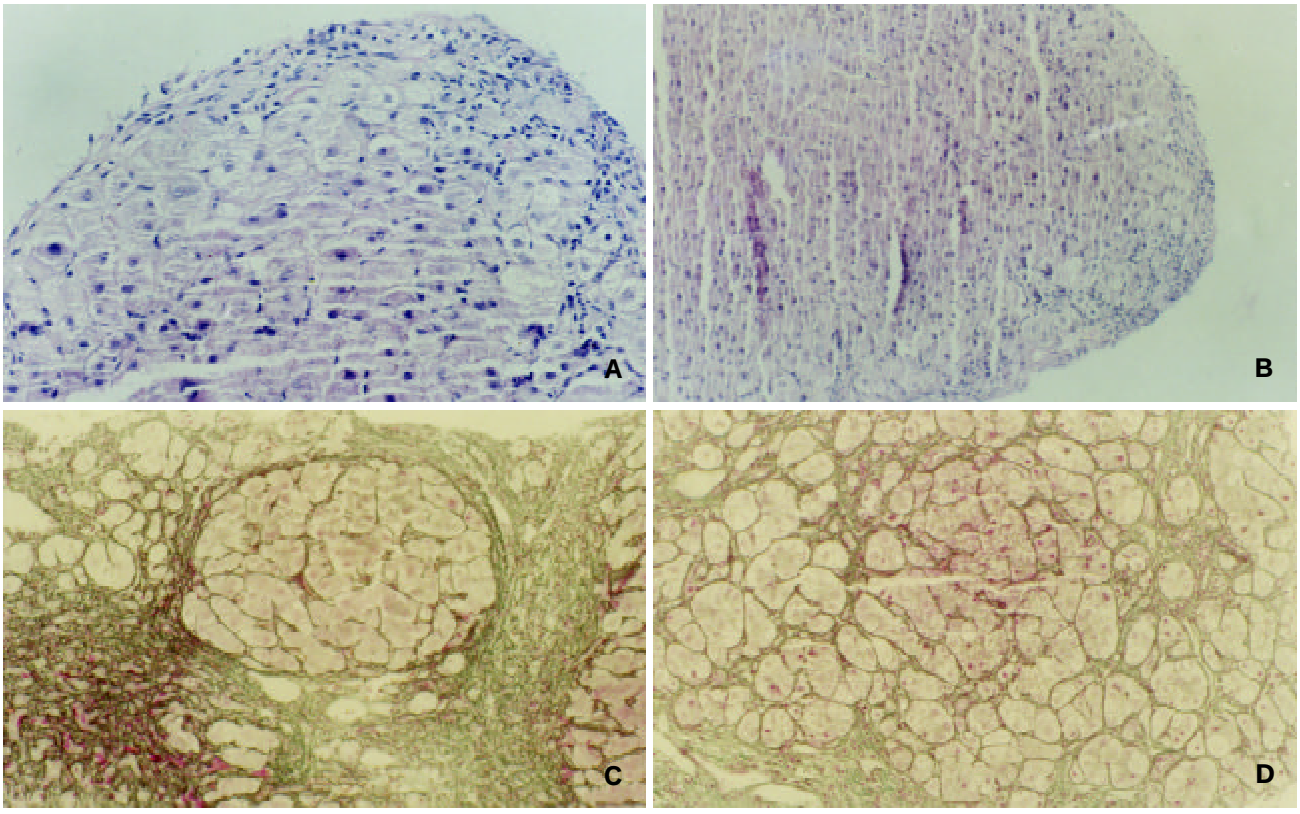

Figure 2 Histological changes of liver biopsy specimens before and after treatment in SA-B group:
A: First liver biopsy (G3, HE stain, ×100) before treatment;
B: Second liver biopsy (G3, HE stain, ×100) after treatment;
C: First liver biopsy (S4, collagen stain, ×100) before treatment;
D: Second liver biopsy (S3, collgen stain,. ×100) after treatment.

Table 2 Correlation between serum fibrotic markers and fibrotic stages

Stages(*n*)	HA(μg/L)	LM(μg/L)	IV-C(μg/L)	PⅢP(μg/L)
S0 (4)	103±67.6	116±34.8	232±148	6.7±2.3
S1 (14)	156±175	103±30	129±92[a,c]	7.4±3.1[a,c]
S2 (31)	197±175	99±26.5	178±138	8.5±4.1[a]
S3 (35)	252±243	107±22	227±123	10.8±4.9
S4 (36)	239±176	108±22.6	232±158	13±7.8

[a]*P*<0.05, *vs* S4; [c]*P*<0.05, S3.

Table 3 Correlation between serum fibrotic markers and inflammatory grades

Grades(*n*)	HA(μg/L)	LM(μg/L)	IV-C(μg/L)	PⅢP(μg/L)
G0 (1)	96	106	212	9.2
G1 (14)	136±161[a,c]	119±26	146±92[a]	6.38±2.4[a,c]
G2 (35)	165±158[a]	96±22	178±128[a]	7.71±3.7[a,c]
G3 (49)	258±216	105±25	211±129	12±5.85
G4 (21)	276±202	107±24	276±178	14±7.44

[a]*P*<0.05, *vs* S4; [c]*P*<0.05, S3.

Changes of liver fibrotic stages and inflammatory grades

Based on the liver fibrotic stages and inflammatory grades before and after treatment, it was rated as improved (alleviated by ⩾1 stage), stable, or deteriorated (⩾1 stage). The improvement rates of inflammatory grades and fibrotic stages were 40.0 % and 36.67 % respectively in SA-B group, which were slighting higher than in IFN-γ group (36.67 % and 30.0 %). Deterioration rates were 16.7 % and 20.0 % in SA-B group, which were much lower than in IFN-γ group (20.0 % and 30.0 %). There was no significant difference between the two groups. Fibrotic stages of 4 patients in SA-B group decreased by 2 stages after treatment. But there was none in IFN-γ group.

Changes of serum fibrotic markers

There was no significant differences in serum HA, LM and P-III-P contents between the two groups before treatment. But the serum IV-C content in SA-B group was obviously higher than that in IFN-γ group before treatment. The average content of serum HA in SA-B group decreased remarkably after treatment ($P<0.05$), and decreased in IFN-γ group, but with no significant difference. The abnormal rate of serum HA content in SA-B decreased from 80 % to 36.67 % ($P<0.05$). But there was no significant difference in the changes of abnormal rate of serum HA content in IFN-γ group. Serum IV-C content decreased remarkably in SA-B group after treatment ($P<0.05$), but it increased in IFN-γ group. There was no significant difference in serum LM and P-III-P contents before and after treatment in both groups. Overall, the first three markers of 9 patients in SA-B group were lowered by ⩾30 % after treatment, but of only one patient in IFN-γ group (Tables 4-6).

Changes of serum liver function

There was no difference in liver function (Alb, globulin, Serum ALT, AST and GGT activities, serum total and direct bilirubin) between the two groups before treatment. Alb was within normal ranges but globulin was much higher than the normal before treatment in both groups. Alb increased significantly after treatment in IFN-γ group ($P<0.05$), but had no change in SA-B group. There was no significant change of globulin before and after treatment in both groups. The abnormally high ALT activities before the treatment in SA-B group decreased significantly in the first month ($P<0.05$) and maintained at low levels in the following months of the treatment. In terms of individual subject, ALT activities of 14 patients (46.67 %) in IFN-γ group and 7 patients (23.33 %) in SA-B group continued to increase after treatment, but with no significant difference between the two groups ($P<0.05$), (Table 7). AST activities decreased after treatment in both groups, but without significant difference (Table 8).

GGT activities decreased after treatment in both groups, without significant difference. Serum total and direct bilirubin content in both groups were close to the upper limit of normal ranges. Total bilirubin contents decreased after treatment in both groups without significant difference. Direct bilirubin contents decreased significantly after treatment in both groups. The remarkable decrease of direct bilirubin in SA-B group started in the 3rd treatment.

Changes of liver ultrasound imaging

There was no obvious change of portal veins and splenic veins before and after treatment in the two groups. SA-B showed an improving tendency based on the score of ultrasound imaging. The scores of only two patients in SA-B group rose (deterioration). But scores of 11 patients increased in the control group. There was significant difference between the two groups ($P<0.05$), (Table 9).

Table 4 Serum HA,LM,IV-C and PⅢP contents before, during and after treatment

		HA(μg/L)	LM(μg/L)	IV-C(μg/L)	PⅢP(μg/L)
IFN-γ group	Before	250±210	94±27	112±64	10.4±5.0
	During	225±248	110±22	219±143	10.2±4.4
	After	185±172	104±26	212±105	8.0±2.8
SA-B group	Before	267±211	103±17	294±155	13.2±8.1
	During	219±243	117±21	248±164	11.9±4.9
	After	169±183[a]	118±24	190±142[b,c]	9.7±5.3

[a]*P*<0.05, [b]*P*<0.01, *vs* before treatment; [c]*P*<0.05, *vs* during treatment.

Table 5 Abnormal rates of serum fibrotic markers before and after treatment (abnormal rate(%) = number of abnormal cases / total cases)

Groups		HA>110μg/L	LN>132μg/L	IV-C>140μg/L	PⅢP⩾5μg/L
IFN-γ	Before	21/30(70%)	1/30(3.33%)	6/30(20.0%)	20/29(68.97%)
	After	17/30(56.7%)	3/30(10.0%)	20/30(66.7%)	25/29(86.2%)
SA-B	Before	24/30(80%)	1/30(3.33%)	24/30(80.0%)	26/28(92.86%)
	After	11/30(36.67%)[a]	7/30(23.23%)	15/30(50.0%)[a]	25/28(89.29%)

[a]*P*<0.05, *vs* before treatment.

Table 6 Decrease of 4 serum fibrotic markers >30 % after treatment in two groups

Groups	Total number	Decrease of 3 markers>30%	Decrease of 2 markers>30%	Decrease of 1 marker>30%
IFN-γ	30	1(3.33%)	6(20%)	13(43.33%)
SA-B	30	9(30%)	7(23.33%)	7(23.33%)

[a]*P*<0.05, *vs* IFN-γ

Table 7 Change of ALT activities before and after treatment *n* (%)

Group	Recovered	Decreased (>50%)	Decreased (<50%)	Stable	Increased
IFN-γ	6(20)	4(13.33)	4(13.33)	2(6.67)	14(46.67)
SA-B	6(20)	5(16.67)	8(26.67)	4(13.33)	7(23.33)[a]

[a]$P<0.05$, *vs* IFN-γ.

Table 8 Change of AST activities before and after treatment *n* (%)

Group	Recovered	Decreased (>50%)	Decreased (<50%)	Stable	Increased
IFN-γ	8(26.67)	3(10.0)	4(13.33)	4(13.33)	11(36.67)
SA-B	7(23.33)	2(6.67)	4(13.33)	5(16.67)	12(40.00)

Table 9 Change of ultrasound image scoring

Groups	*n*	Before treatment	After treatment	Improved *n* (%)	Deteriorated *n* (%)
IFN-γ	29	5.38±1.52	5.75±1.45	4(13.79)	11(37.93)
SA-B	30	5.10±1.52	4.70±1.44	9(30)	2(6.67)[a]

Comparison of χ^2 test between two groups, [a]$P<0.05$

Changes of serum viral markers

HBsAg of each patient in both groups was positive before treatment. No changes happened for HBsAg/anti-HBs after treatment. HBV-DNA of 4 patients in each group became negative after treatment. HBeAg of 13 patients in IFN-γ group and of 15 patients in SA-B group were positive before treatment. But after treatment, 4 patients in IFN-γ group and 3 patients in SA-B group became negative. And at the same time, 2 patients in each group were positive in anti-HBe.

Changes of symptoms and signs

After 6 months treatment, major symptoms and signs such as anorexia, general fatigue, weakness and soreness in lumbar regions and knees, insomnia, yellow urine and hypochondriac pain were remarkably relieved in both groups.

Side effects and safety

The results of EKG, renal function, regular blood test and regular urine test showed no change during the treatment in SA-B group. There were no side effects or negative responses in SA-B group. Fifteen patients in IFN-γ group had fever at the beginning of the treatment. One patient was unable to tolerate the side effect, thus terminating the trial. The other patients succeeded in finishing the clinical trial after the disappearance of fever. One patient in IFN-γ group had transient decrease of leukocytes. Under careful observation, the patient recovered after treatment (without stopping drug administration or using special treatment). No other side effect was noticed.

Analysis of factors affecting anti-fibrotic treatment effect

Histopathological fibrotic stages before and after treatment were the evidence for evaluating the drug efficacy. It was divided into improved, stable and deteriorated groups. The analysis of liver function and serum fibrotic markers before treatment showed that the effect of SA-B in anti-fibrosis was related to the level of liver injury before treatment. The patient having regression of fibrosis after treatment had much lower ALT and AST activities and total bilirubin content before treatment than those having aggravation of fibrosis after treatment. There was no obvious correlation among the above factors in IFN-γ group (Tables 10 and 11).

Table 10 Correlation between change of fibrotic stages before and after treatment,liver function and serum fibrotic markers before treatment in SA-B group

Items	Improved(*n*=11)	Unchanged(*n*=13)	Deteriorated (*n*=6)
Albumin(g/L)	40±4.4	39.3±6.5	39.5±3.0
Globulin(g/L)	31.1±6.7	33.9±6.9	30.9±8.5
ALT(U)	64±41 [a]	108±83	201±155
AST(U)	48±29 [b]	73±55 [a]	155±108
GGT(U)	72±44	99±47	96±54
Total bilirubin(mMol)	14.9±3.9[b]	15.0±6.6[a]	21±10
Direct bilirubin(mMol)	2.9±1.7	3.1±2.3	5.0±4.0
HA(μg/L)	172±110	292±188	386±330
LN(μg/L)	106±10	107±21	91±18
IV-C(μg/L)	248±88	352±176	284±164
PⅢP(μg/L)	10.2±6.8	14.8±7.3	15±10.2

Compared with elevation of stages,[a]$P<0.05$, [b]$P<0.01$

Table 11 Correlation between change of fibrotic stages before and after treatment, liver function and serum fibrotic markers before treatment in IFN-γ group

Items	Improved(*n*=9)	Unchanged(*n*=12)	Deteriorated (*n*=9)
Albumin(g/L)	39.9±5.0	40.8±4.6	40.6±6.7
Globulin(g/L)	28.1±4.6	30.7±4.0	31.9±5.3
ALT activities(U)	94±56	79±51	171±286
AST activities(U)	77±53	56±33	80±73
GGT activities(U)	76±41	76±48	81±40
Total bilirubin(mMol)	13.4±7.6	16.5±6.4	18.9±7.0
Direct bilirubin(mMol)	3.0±2.2	3.6±2.5	3.3±2.0
HA(μg/L)	219±230	284±246	237±145
LM(μg/L)	97±34	87±18	102±30
IV-C(μg/L)	128±84	104±56	92±32
PⅢP(μg/L)	12.0±6. 2	9.1±5.5	10.9±2.3

DISCUSSION

The hepatic fibrosis is the important pathological feature of chronic liver diseases, which is characterized by HSC activation and the overproduction of extracellular matrix[20-36]. Therefore, inhibition or reversion of hepatic fibrosis is one of the main therapeutic strategies[37-50]. In this study, we found the SA-B effect on liver fibrosis in hepatitis B for the first time, through the double blind trial with IFN-γ as control drug and the observation of liver histopathology, serum fibrotic markers, liver function, liver ultrasound imaging, and symptoms and signs before and after treatment.

SA-B could effectively reverse fibrosis in hepatitis B

The 10th International Congress of Gastroenterology, Los Angeles, September 1994 suggested the etiological base in terms of the diagnosis of chronic hepatitis, making inflammatory grading criteria according to the severity of histological inflammatory necrosis and fibrotic stage standards according to the level of liver fibrosis. Currently liver biopsy is still the "Gold Standard" for scoring fibrosis. But the great

difference in the same liver specimens limited the value of biopsy, making it difficult to evaluate the fibrosis generally and correctly. Liver ultrasound imaging could reflect the specific images of fibrosis. Semi-quantitative evaluation of liver fibrosis and cirrhosis was simple and easily accessible. It was beneficial in the general evaluation of fibrosis, but it failed to precisely reflect the anti-fibrotic effect of the drug because of the insufficiency of quantitative determination. At the same time, multiple factors would affect serum fibrotic markers in the evaluation. It was favorable to combine multiple methods in evaluation. Total 120 biopsy specimens before and after treatment showed that serum fibrotic markers generally rose with the aggravation of fibrotic stages and inflammatory degrees. But the dispersion degree was large. The correlation was better in HA, IV-C and P-III-P. And LM was generally within the normal ranges.

Adapting to the current situation in diagnosis of liver fibrosis, histological fibrotic stages before and after treatment were fundamental in the evaluation of the efficacy in this trial. Improvement rates of fibrotic stages and inflammatory grades were 36.67 %(11/30) and 40 %(12/30) in SA-B group, and were 30 %(9/30) and 36.67 %(11/30) in IFN-γ group, with no significant differences between the two groups. Fibrotic stages of 4 patients decreased more than 2 stages in SA-B group, but none in IFN-γ group. HA and IV-C contents decreased significantly after treatment in SA-B group (P<0.05). The abnormal rate of HA was lowered from 80 % to 36.67 % in SA-B group (P<0.05). In the overall analysis of 4 serum fibrotic marker, 9 patients (30 %) in SA-B group had simultaneous decrease of 3 markers, better than one patient in IFN-γ group. Scores of liver ultrasound imaging with 2 patients in elevation in SA-B group was better than in IFN-γ group with 11 patients in elevation, with significant difference. General analysis of liver biopsy, serum fibrotic markers and ultrasound imaging showed superior effect of SA-B to IFN-γ.

There was no significant change in HBV antigen and antibody systems after treatment in both groups. Anti-fibrotic effect of SA-B or IFN-γ was not related to anti-viral effect. Both drugs were favorable in the relief of symptoms and signs.

Factors affecting anti-fibrotic effect of SA-B

After categorizing the changes of histological fibrotic stages, we analyzed the factors affecting anti-fibrotic effect of SA-B through the analysis of serum fibrotic markers and liver functions before treatment. Before treatment, ALT and AST activities and total bilirubin contents in fibrosis improvement group were significantly lower than those in fibrosis aggravation group. The effect was not related to the contents of serum fibrotic markers before treatment. Severity of liver inflammatory injury was the major factor affecting the anti-fibrotic effect of SA-B. SA-B had a satisfactory effect in regression of fibrosis with minor liver injury prior to treatment, but had no favorable results for severe liver injury prior to treatment. The fibrotic stage was not the major factor affecting the anti-fibrotic effect. There was no relationship in IFN-γ group. The result was instructive in the clinical application of SA-B. It was good anti-fibrotic effect in the treatment of fibrosis patients with minor inflammatory injury.

No side effects or toxicity of SA-B

There was no obvious negative response in SA-B group during the whole treatment. It showed high security in the 6-month administration. Fever and transient decrease of leukocytes were noticed in IFN-γ group.The rate of fever occurrence was 50 %, but it did not affect the completion of the whole treatment.

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