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— Multi-Center Trial —

A multicenter randomized controlled clinical trial of Shosaiko-to in chronic active hepatitis

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Summary: The efficacy of Shosaiko-to (SST) on 222 patients with chronic active hepatitis was studied in a double-blind multicenter clinical study. One hundred and sixteen patients received SST in a daily oral dose of 5.4 g for 12 weeks, followed by the same dose for a further 12 weeks. One hundred and six patients received a placebo containing 0.5 g of SST for 12 weeks, followed by a cross-over to SST for a further 12 weeks. Among the liver tests, serum AST and ALT values decreased significantly with the admisnistration of SST. The difference of the mean value between the SST group and the placebo group was significant after 12 weeks. In patients with chronic active type B hepatitis, a tendency towards a decrease of HBeAg and an increase of Anti-HBe antibodies was also observed. No remarkable side effects were noticed. *Gastroenterol Jpn 1989;24:715–719*

Key words: *chronic active hepatitis; Shosaiko-to*

Introduction

Shosaiko-to (SST) is a traditional Chinese herb medicine (XIAO-CHAI-HU-TANG) and contains Saikosaponin, and Saikosapogenin, an anti-inflammatory agent[1]. It is made from the infusion of 7 species of medicinal plants. Clinically, SST has been used orally in the treatment of various chronic diseases, especially chronic hepatitis, because SST seems to improve liver tests and subjective symptoms such as abdominal discomfort and poor appetite. It has been reported that SST protects hepatic injury induced by CCl_4[2], and has recently been regarded as a biological response modifier, because it augments humoral and cellular immunity[3,4]. Although the clinical usefulness of SST for chronic hepatitis has been widely accepted in Japan, there are few controlled studies using SST for chronic hepatitis. Recently Muzuta et al[5] conducted a controlled double-blined study using SST on 63 chronic hepatitis patients for 8 weeks, and found an improvement in subjective symptoms as well as in some liver tests. The present study attempts to elucidate the efficiency of SST in 222 cases of biopsy-proven chronic active hepatitis with respect to liver functions and also hepatitis viral markers.

Patients and Methods

Two hundred and twenty-two out-patients

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from 42 hospitals were studied from May 1986 to April 1988 giving informed consent. From the results of liver biopsies performed within one year of the beginning of the study, the patients were diagnosed as having chronic active hepatitis. Any treatment with other drugs including corticosteroids, azathioprine, interferon, adenine arabinoside and glycyrrhizine was discontinued 3 months prior to and during the study. Patients with renal disease, diabetes, and those who were pregnant or suffered from alcohol abuse were also excluded.

The drugs used in this study were EK 9 (Kanebo Pharmaceutical Co., Tokyo), which contained 0.9 g of SST per g of fine granules or a placebo, of identical appearance and smell, which contained 0.09 g of SST per g of lactose. The daily oral dose of each drug was 6 g. Two grams of the drug was taken 3 times daily, before or between meals for 12 weeks, followed by a further 6 g per day of EK 9 for both groups for 12 weeks, if the patients consented to continue the study. The coding of the medications for assignment to the patients was done by a controller and the medications were randomly assigned to the patients. Clinical examinations were performed prior to and at the beginning of the study as well as at 4, 8, 12, 16, 20, and 24 weeks.

The clinical data, including subjective symptoms and various liver tests, were carefully evaluated. Hepatitis B markers were tested on HBsAg, anti-HBs antibodies, HBeAg and anti-HBe antibodies. The HBeAg titer was expressed as a cut-off index and the anti-HBe antibody was expressed as an inhibition percentage. A value of HBeAg above 2 was considered as positive, and the borderline value between 1.0 to 1.9 was also considered to be positive if the anti-HBe titer was below 30% inhibition. A value of anti-HBe titer above 70% was considered as positive[6,7]. Hematological and urinary tests were also done.

The data were statistically analyzed using the χ^2 test, paired t-test and t-test, and examined for significance at the 5% and 1% significance levels.

Table 1 Main clinical and laboratory findings

	Shosaiko-to	Placebo
Number of Cases	116	106
Sex ratio (M:F)	85:31	78:28
Age <20	1	2
20-29	11	19
30-39	26	24
40-49	27	20
50-59	30	27
>60	21	14
Past history		
Acute hepatitis	11	9
Blood transfusions	17	17
HB marker		
HBsAg positive	52	47
HBeAg positive	33	32
anti-HBe positive	13	4
Liver function tests		
Bilirubin (mg/dl)	0.81±0.35	0.83±0.41
AST (I.U.)	114±64	119±102
ALT (I.U.)	175±113	177±146
γGTP (U.)	77±77	73±56
Albumin (g/dl)	4.1±0.4	4.2±0.4
γglobulin (g/dl)	1.49±0.43	1.45±0.39

Results

The study started with 222 patients. The clinical and laboratory findings of the patients in both groups are summarized in **Table 1**. There were no significant differences between both groups with respect to sex ratio, age, past history, HB markers or liver tests. The study was discontinued in 18 cases, of which 12 cases were in the SST group and 6 cases were in the placebo group. In the SST group, the reasons for discontinuance of the study were that 6 cases did not visit the hospital, 3 cases were using other drugs, 2 cases had aggravated results by liver tests and 1 case had an improved liver test. In the placebo group, the reasons for discontinuance of the study were that 3 cases did not visit the hospital and 3 cases were using other drugs. After 12 weeks of the study, a further 12 weeks study was conducted in about 72% of the original patients.

Among various lier tests, serum values of AST, ALT and γGTP changed significantly. As shown in **Figure 1**, serum AST values decreased

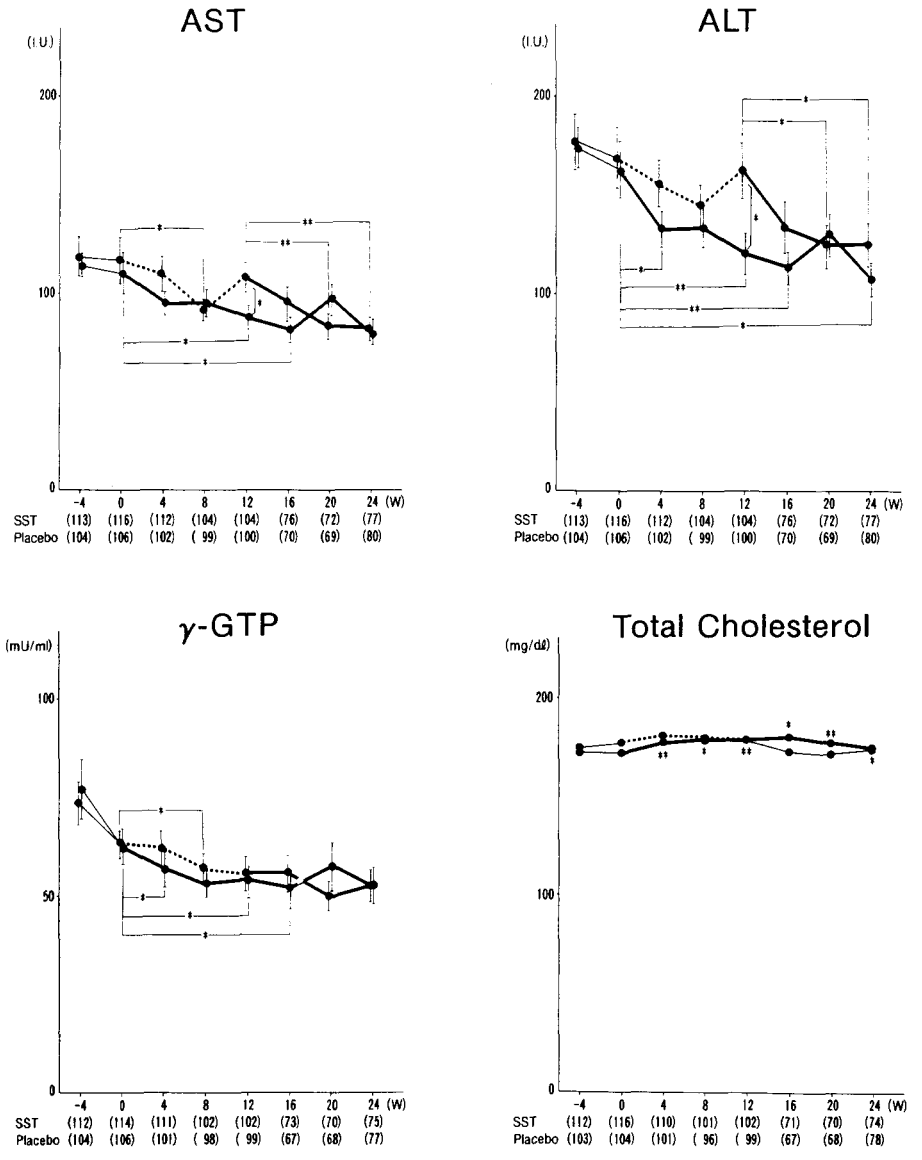

Fig. 1
Changes in serum levels of AST, ALT, γGTP and cholesterol during the study
●——● SST
●- - -● Placebo
●——● Before administration
*P<0.05, **<0.01
( ): no. of cases

at 12 and 16 weeks in the SST group, while the placebo group had a transitory decrease at 8 weeks. In the period following the SST cross-over in the placebo group, the AST values also decreased at 8 (20) and 12 (24) weeks (the figures in the brackets indicate the number of weeks from the beginning of the experiment). The mean values of both groups became significantly different at 12 weeks, but were almost the same at 24 weeks. Similarly, serum ALT values decreased at 4, 12, 16 and 24 weeks in the SST group, and at 8 (20) and 12 (24) weeks in the placebo group, after the cross-over. However, it did not decrease significantly in the placebo group. The mean values became significantly diffierent at 12 weeks. Serum γGTP values also had the same tendency but were less prominent, because the mean values never became significantly different in the both groups.

In patients with active chronic type B hepatitis, serial changes of HBeAg and anti-HBe titer are shown in **Figure 2**. HBeAg significantly decreased at 12 and 24 weeks in the SST group, and also at 12 weeks in the placebo group. Anti-

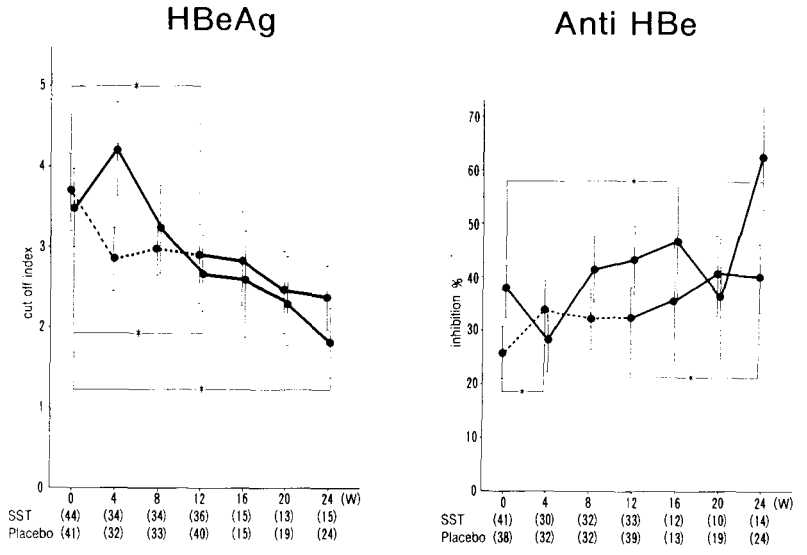

Fig. 2
Changes in serum levels HBeAg and anti-HBe antibody during the treatment
SST
Placebo
*P<0.05
( ): no. of cases

HBe antibodies significantly increased at 24 weeks in the SST group, and at 12 weeks following the cross-over in the placebo group. It also significantly increased at 4 weeks in the placebo group. However, the mean values of HBeAg and anti-HBe never became significantly different in both groups. Likewise, the incidence of a seroconversion from HBeAg to anti-HBe, a seronegativity for HBeAg and 50% reduction of HBeAg titer was not significantly different between both groups.

In the remaining laboratory tests, serum electrolytes did not change in both groups, however, the serum cholesterol level increased minutely in the SST group and the increase was significant (**Fig. 1**). The hematological hematocrit and hemoglobin values also increased significantly at 12 and 24 weeks in the SST group. However the mean vales never became significantly different. The reason for these reflect an increased appetite by the SST group[5]. No significant changes were observed in the other oaboratory tests.

The side effects in the SST group consisted of 2 cases of nausea, 2 cases of anorexia, 1 case of general fatigue, 1 case of abdominal fullness 1 case of diarrhea and 1 case of paresthesia, whereas in the placebo group, there was 1 case with an oppressive sensation in the right hypochondrium and 1 case of elevated blood pressure. Although these side effects rarely and mildly appeared, digestive symptoms were often observed in the SST group.

Discussion

SST, a traditional Chinese medicine is widely used in the clinical treatment of chronic infections, nephritis and hepatitis. According to Chinese medicine, SST improves subjective symptoms, especially digestive discomfort. A previous controlled study conducted by Mizuta et al[5] revealed that SST improved subjective subjective symptoms such as nausea, vomiting and discomfort in the right hypochondrium in patients with chronic hepatitis. The reason as too why SST is widely used in Japan for the treatment of chronic hepatitis is partly due to an improvement of subjective symptoms associated with chronic hepatitis. In addition, the side effects of SST that have been reported are minute. The present study, however, found some digestive discomfort in some patients in the SST group. Due to the fact that Chinese medicine emphasizes that individual responses to SST are due to constitutional differences, further medical analysis is required.

The present controlled study revealed that

SST lowered serum levels of AST, ALT and γGTP in chronic active hepatitis, suggesting that SST improves some inflammatory processes in the liver. Because the SST effect on liver tests is not so marked, it is uncertain whether liver test improvements are actually accompanied by a histological improvement in the liver. As shown in **Table 1**, chronic active hepatitis in Japan is caused mostly by the hepatitis virus, so that the SST effects on serum enzyme activity may be attributed either to the suppression of the inflammatory process or to the reduction of viral infection. In fact, Saikosaponin, one of principal elements of SST, has an anti-inflammatory role[1] and a stabilizing effect on cell membranes[8], which seem to be responsible for its favorable effect on chronic active hepatitis.

Although the immunopharmacological functions of SST have not yet been completely clarified, it has been reported that SST augments polyclonal ctivation of human peripheral B cells by pokeweed mitogen[9] and SST cuases the accumulation of immature B cells and null cells and activates macrophages in the peritoneal cavity[3,4]. According to the present study, SST has no significant effect on the HBeAg/anti-HBe system in active chronic type B hepatitis, but there was a tendency for HBeAg to decrease and anti-HBe antibodies to increase in the SST group. To evaluate the efficiency of SST on HB markers, further precise studies should be carried out in a large number of patients.

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