Pharmacoepidemiological study of the clinical efficacy of Sho-saiko-to (Xiao-Chai-Hu-Tang) in chronic liver disease patients

Tomohide AKASE,*[a,b] Shin-ichi TASHIRO,[b] Akira ISHIBASHI,[c] Tomoko AKASE,[b] Masakazu KANEKO,[d] Yasuhiro KOMATSU,[e] Ken-ichi SAGAWA,[a] Shigehiko SHIMADA[a]

[a] *Department of Pharmacy, Kitasato University Hospital,* [b] *Department of Clinical and Biomedical Sciences, Showa Pharmaceutical University,* [c] *Department of Urology, Kitasato University School of Medicine,* [d] *Medical Support Business Unit, BELLSYSTEM24, Inc.* [e] *Department of Serology Kanazawa Medical University*

(*Received January 11, 2001. Accepted April 5, 2001.*)

Abstract

The effect of Sho-saiko-to (Xiao-Chai-Hu-Tang, 小柴胡湯) on liver functions was examined using the technique of pharmacoepidemiology. The subjects were all 609 outpatients at Kitasato University Hospital who were continuously treated for liver diseases by a Kampo medicine, Sho-saiko-to and received medical examinations between September, 1995 and September, 1996. Three hundred and fifteen patients who stopped using Sho-saiko-to in March, 1996 and continued taking other prescription drugs were designated as the Sho-saiko-to terminated group (STG). Two hundred and ninety-four persons who continued treatment by Sho-saiko-to throughout the investigation period were designated as the Sho-saiko-to continuing group (SCG). The changes in the liver function in the two groups were observed. By using Sho-saiko-to, the serum AST level decreased from the abnormally higher value, 75.2±3.9 and 69.8±4.2 IU/L at the starting point of this survey to 28.5±1.0 and 36.6±1.6 IU/L within normal range in March, 1996 in STG and SCG, respectively. In SCG they successively decreased during the follow-up period to 30.4±1.5 IU/L in September, 1996. However, the value in STG significantly increased over the value of the starting point to 98.8±11.0 IU/L after terminating Sho-saiko-to therapy. Similar to AST, the ALT value in SCG also decreased from 79.9±5.2 to 44.5±2.0 and 33.2±1.7 IU/L in September, 1995, March and September, 1996, respectively. On the other hand, those in STG changed from 81.0±4.0 to 35.8±1.6 and 98.1±5.1 IU/L, respectively. In almost all patients belonging to this group the AST and ALT levels became worse. Only 6 patients (1.9 %) kept the gradual decrease of AST and ALT levels and the patients with the AST and ALT values over 100 IU/L increased from 1.6 and 1.9 % in March, 1996, to 21.9 and 28.6 % within only 6 months, respectively. Compared to the STG, the SCG also showed better control in the levels of γ-GTP, LDH, ALP, total bilirubin and cholinesterase. No significant change was observed in the total cholesterol, serum albumin, or total protein values. Serious adverse reaction such as pneumonia was not observed in either group in the present investigation. Attention should be paid to adverse reactions including interstitial pneumonia during Sho-saiko-to treatment but, on the other hand, we should abstain from giving questionable informations which promotes noncompliance.

Key words Sho-saiko-to (Xiao-Chai-Hu-Tang), chronic liver disease, pharmacoepidemiology.

Abbreviations SCG, Sho-saiko-to continuous treatment group; STG, Sho-saiko-to terminated group; IDAR, information on drug adverse reactions; UDSI, urgent drug safety information.

*〒194-8543 東京都町田市東玉川学園3-3165
昭和薬科大学病態科学 赤瀬朋秀
3-3165, Higashi-Tamagawa-Gakuen, Machida, Tokyo 194-8543, Japan

和漢医薬学雑誌 18, 95－106, 2001

Introduction

Sho-saiko-to (Xiao-Chai-Hu-Tang, 小柴胡湯) has been used for the treatment of liver dysfunction such as chronic hepatitis and this drug is one of the most widely prescribed Kampo medicines (Sino-Japanese traditional herbal medicine). A double blind clinical trial revealed the usefulness of Sho-saiko-to for active chronic hepatitis[1-3] and the authors of those reports concluded that it is an excellent drug for the treatment of hepatitis. Oka *et al.*,[4,5] reported that Sho-saiko-to suppressed the incidence of hepatic cancer among the patients with chronic hepatitis from a 5-year follow-up survey, and they stressed the usefulness and importance of this drug for hepatitis therapy and the prevention of liver cancer from the points of view of medical economy and clinical importance. But since the first case when interstitial pneumonia was thought to be associated with Sho-saiko-to use was reported by Tsukiyama *et al.*[6] in 1989, similar clinical case reports have been published. The Information on Drug Adverse Reactions (IDAR) No.107,[7] released by the Japanese government's Ministry of Health and Welfare, reported the incidence of interstitial pneumonia in patients who had received Sho-saiko-to, in a report entitled "Interstitial Pneumonia and Sho-saiko-to." No.118[8] of this publication reported that the same adverse reaction occurred in the patients with chronic hepatitis treated with a combination of interferon-α and Sho-saiko-to. In addition, in IDAR No. 137,[9] it was concluded that this interstitial pneumonia was a serious side effect of Sho-saiko-to, and the Ministry of Health and Welfare warned of this in Urgent Drug Safety Information (UDSI) in 1996.

The causal relationship between the interstitial pneumonia and Sho-saiko-to and the mechanism of pathogenesis has not yet been clarified, although it has been studied and discussed by an increasing number of clinicians and researchers, and the early resolution of this adverse reaction is desirable.

On the other hand, the number of Sho-saiko-to prescriptions has sharply decreased since March 1996 when the news media reported 10 cases of death due to interstitial pneumonia among about one to two million patients who had received of Sho-saiko-to. The number of patients and clinicians who wish to use Sho-saiko-to for hepatitis treatment has greatly decreased, and the noncompliance has increased. However, there is concern about the prognosis of patients who suddenly stop the Sho-saiko-to intake without completing the treatment until the proper end point. Therefore, in this report the therapeutic effects are compared between groups of patients who continued and stopped the treatment, with laboratory values such as blood aminotransferase levels in the patients as the markers of the follow-up survey.

Subject patients and Methods

The subjects of this study were all outpatients treated with Sho-saiko-to and followed the liver functions by clinical tests at Kitasato University Hospital continuously from September 1995 until September 1996. In addition, they received the same medication except for Sho-saiko-to. The subjects, 609 patients, were divided into two groups. One was the Sho-saiko-to continuous treatment group (SCG), in which 294 patients were continuously medicated with the same drugs, and the other was the Sho-saiko-to terminated group (STG), in which 315 patients stopped taking Sho-saiko-to in March, 1996 but continued taking their other medications. The clinical efficacy of Sho-saiko-to was evaluated by the serum laboratory test values of L-aspartate : 2-oxoglutarate aminotransferase (AST), L-alanine : 2-oxoglutarate aminotransferase (ALT), γ-glutamyl transpeptidase (γ-GTP), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), total bilirubin, cholinesterase, total cholesterol, total protein and serum albumin as the markers of liver function. Laboratory examinations were carried out at five points, that is, in March, 1996, and three and six months before and after. Differences between the groups were compared using the Mann-Whitney U and Wilcoxon's signed rank test, and recognized significant if $p<0.05$.

Results

Patient background

Fifty one point seven percent of the total patients (309/609) were male and 49.3 % (300/609) were

Table I Patient background: Sex and Age

	STG	SCG	TOTAL
Sex			
male	159	150	309 (50.7%)
female	156	144	300 (49.3%)
total	315 (51.7%)	294 (48.3%)	609(100.0%)
Age			
−19	19	16	35 (5.7%)
20−29	22	25	47 (7.7%)
30−39	28	41	69 (11.3%)
40−49	46	26	72 (11.8%)
50−59	66	77	143 (23.5%)
60−69	65	62	127 (20.9%)
70−	69	47	116 (19.0%)
total	315 (51.7%)	294 (48.3%)	609(100.0%)

female. The sex and age distribution of patients is shown in Table I. There were no differences between the two groups, STG and SCG, on the total number and sex distribution of patients. About two-thirds of the patients were over 50 years of age and 40 % of the patients were over 60 years of age. The patients over 60-years-old constituted about 40 % in either group, and no remarkable difference in the age distribution was recognized in the groups (Table I). The diseases in the patients are listed in Table II. In Kitasato University Hospital, Sho-saiko-to was administered to almost all patients based on the diagnosis. About three fourths of the Sho-saiko-to-given patients had hepatic disorders. Seventy six point eight percent of the patients with hepatic disorders were given Sho-saiko-to. The major diseases among these 468 patients were chronic hepatitis (27.1 %), followed by hepatic cancer (5.1 %), fatty liver (4.2 %), liver cirrhosis (2.0 %) and alcoholic hepatitis (0.8 %). However, Sho-saiko-to was prescribed mainly (37.6 %) for the patients with relatively mild hepatic dysfunction who were diagnosed only by the elevated serum aminotransferase activities using the conventional clinical examinations. The clinical examinations of virus infection were not performed in 303 cases (64.8 %) out of 468 with hepatic disorders and the remaining patients (35.3 %) who received the tests were HBV and/or HCV positive (Table II). Most of the patients

Table II Patient background: Diagnosis and Virus Test

		STG	SCG	TOTAL
hepatic diseases	liver function deterioration	125	104	229 (37.6%)
	chronic hepatitis	84	81	165 (27.1%)
	liver cancer	17	14	31 (5.1%)
	fatty liver	13	13	26 (4.2%)
	cirrhosis of liver	7	5	12 (2.0%)
	alcoholic hepatitis	3	2	5 (0.8%)
	total	249	219	468 (76.8%)
non-hepatic diseases	gastrointestinal disease	28	33	61 (10.1%)
	respiratory disease	28	31	59 (9.7%)
	atopic dermatitis	6	5	11 (1.8%)
	pustulosis palmo-plantaris	1	2	3 (0.5%)
	idiopathic thrombocytopenic purpura	1	1	2 (0.3%)
	others	2	3	5 (0.8%)
	total	66	75	141 (23.2%)
	sum total	315	294	609(100.0%)
tests of hepatitis viruses	HBV+	20	20	40
	HCV+	59	60	119
	HBV&HCV+	5	1	6
	not examined	165	138	303
	total	249	219	468

Table III Patient background: Drug therapy

		STG	SCG	TOTAL
Sho-saiko-to only		269	272	541 (88.9%)
with glycyrrhizin pharmaceutical drugs		26	8	34 (5.6%)
with ursodesoxycholic acid		6	4	10 (1.6%)
Combination with other drugs for hepatic diseases*		14	10	24 (3.9%)
total		315	294	609(100.0%)
history of interferon treatment usage	received	5	0	5 (0.8%)
	not received	310	294	604 (99.2%)
total		315	294	609(100.0%)

*Other drugs: consist of glutathione, thiopronine and liver hydrolysate medicine

(about 90 %) were treated with Sho-saiko-to as the single medication (Table III). Only 5 patients (0.8 %) had a history of interferon treatment. They were all belonging to the STG and there was no case in which a patient received the interferon treatment in the SCG.

Comparison of hepatic function changes between SCG and STG

The changes of hepatic function were followed from September 1995 to September 1996 in both groups. In this study, all laboratory examination values were expressed as the mean±S.E., and probability was based on the laboratory examination value in March, 1996. The serum AST levels, shown in Fig. 1, decreased from the abnormally higher values at the starting point of this survey to normal ranges in

Table IV The change of serum AST and ALT levels in STG by terminating the Sho-saiko-to therapy for 6 months

	AST		ALT	
	1996.3.	1996.9.	1996.3.	1996.9.
IU/L	person %	person %	person %	person %
0-100	310 (98.4)	246 (78.1)	309 (98.1)	225 (71.4)
101-200	5 (1.6)	44 (14.0)	5 (1.6)	58 (18.4)
201-300	0	13 (4.1)	1 (0.3)	22 (7.0)
301-400	0	6 (1.9)	0	6 (1.9)
401-500	0	3 (1.0)	0	3 (1.0)
501-	0	3 (1.0)	0	1 (0.3)

*The number and percentage of patients are shown

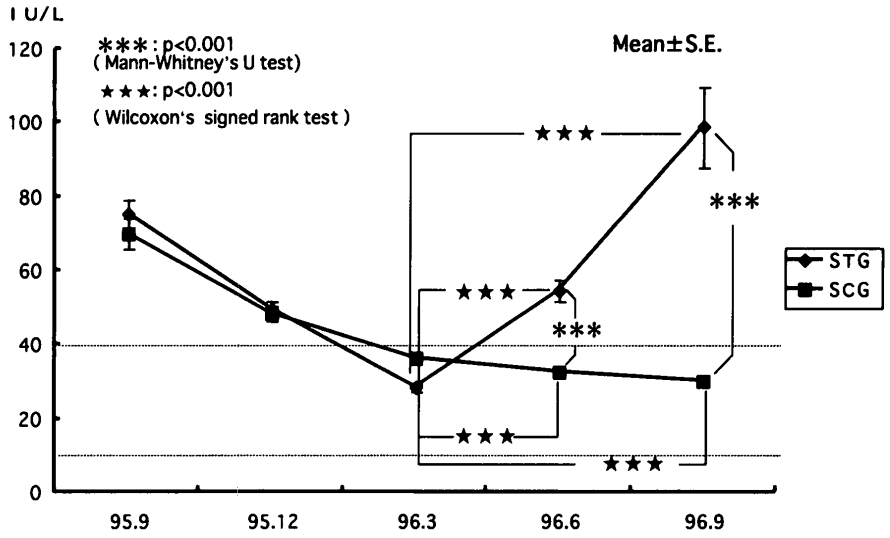

Fig. 1 Liver function (AST) of the Sho-saiko-to terminated group and continuous treatment group

March, 1996 in both groups by using Sho-saiko-to. The mean value of AST level in SCG was successively decreased throughout the follow-up period. This indicated that continuous Sho-saiko-to treatment was effective for maintaining the normal hepatic function. On the other hand, however, the values in STG significantly increased after the Sho-saiko-to treatment ceased and it was over the value of the starting point in September, 1996. In almost all patients belonging to this group, except for only six patients (1.9 %), the AST level worsened. As shown in Table IV, the patients with the AST level over 100 IU/L were 1.6 % in March but 21.9 % in September, 1996. Similarly, the ALT level (Fig. 2) decreased from abnormal value to the normal range until March, 1996 in both groups but only in the STG the value became worse after terminating the Sho-saiko-to therapy. The patients were divided into two groups, those with serum ALT level

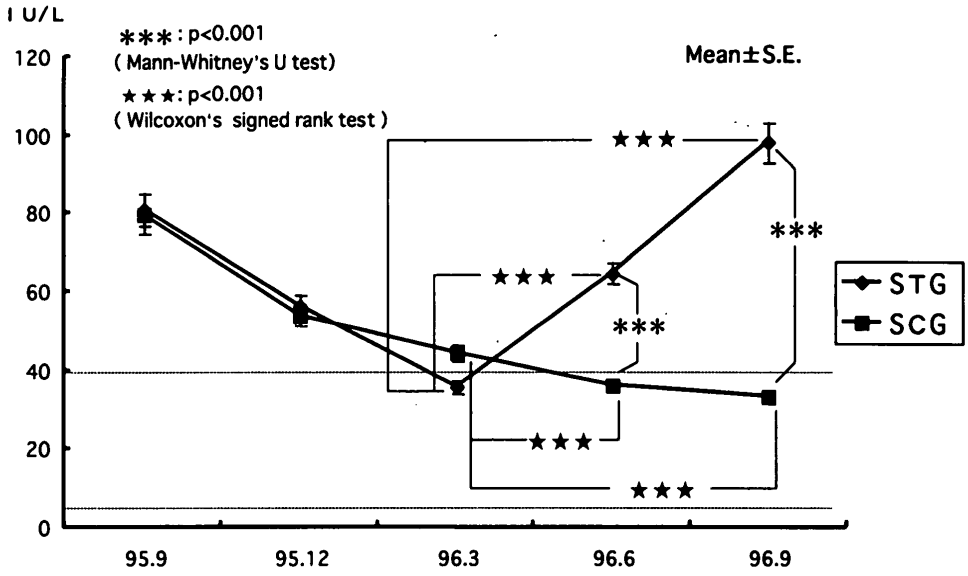

Fig. 2 Liver function (ALT) of the Sho-saiko-to terminated group and continuous treatment group

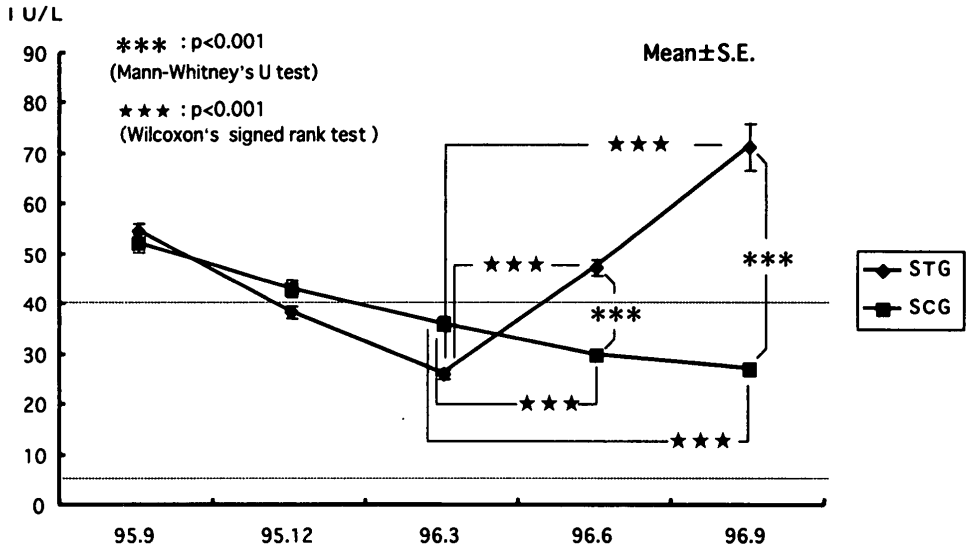

Fig. 3 Liver function (ALT) of the Sho-saiko-to terminated group and continuous treatment group -for patients with ALT<100-

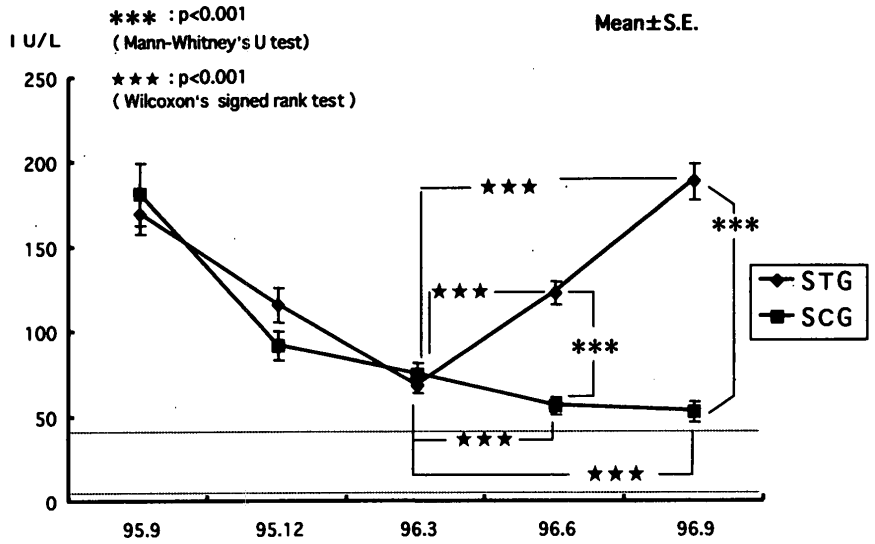

Fig. 4 Liver function (ALT) of the Sho-saiko-to terminated group and continuous treatment group -for patients with ALT≧100-

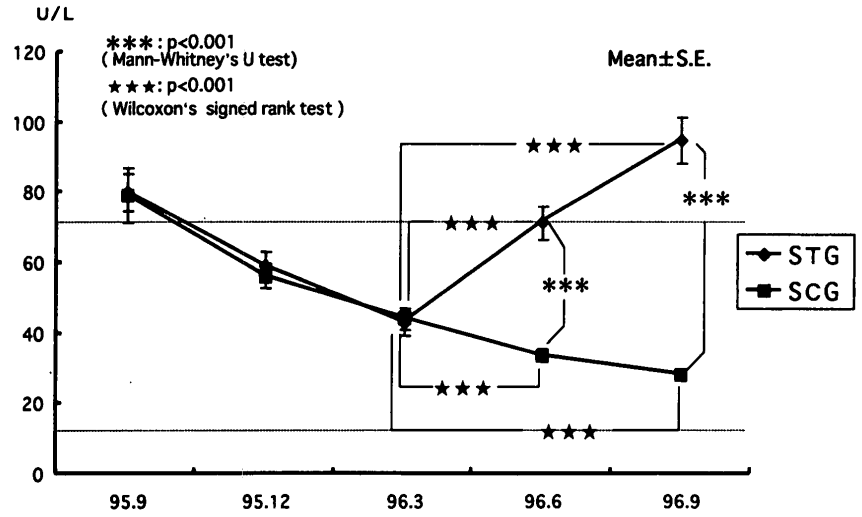

Fig. 5 Liver function (γ-GTP) of the Sho-saiko-to terminated group and continuous treatment group

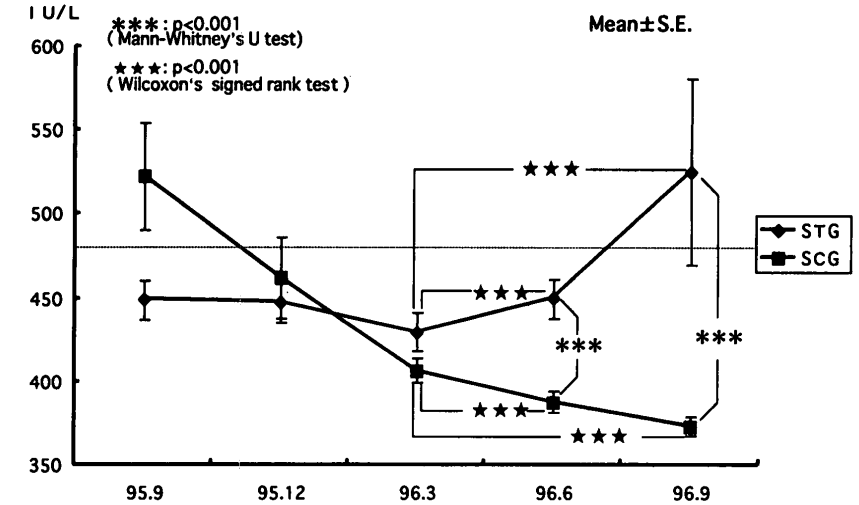

Fig. 6 Liver function (LDH) of the Sho-saiko-to terminated group and continuous treatment group

over 100 units and those with less than 100 units in March, 1996, and the change of serum ALT level was investigated. Only six patients (1.9 %) kept the gradual decrease of ALT and the patients with the ALT level over 100 IU/L increased from 1.9 % on March, 1996 to 28.6 % within only six months (Table IV).

The Sho-saiko-to treatment also decreased the serum γ-GTP levels from the beginning of treatment to March 1996 (Fig. 5). The γ-GTP levels in SCG and in STG were 44.2±3.0 U/L and 43.1±3.5 U/L, respectively, in March, 1996. The SCG patients showed a good control of γ-GTP, as shown by the fact that the serum γ-GTP levels were 33.9 ±1.9 U/L ($p<0.0001$) in June and 36.1±1.6 U/L ($p<0.0001$) in September, compared to the levels in March, 1996. But the serum levels of γ-GTP conversely increased in the STG.

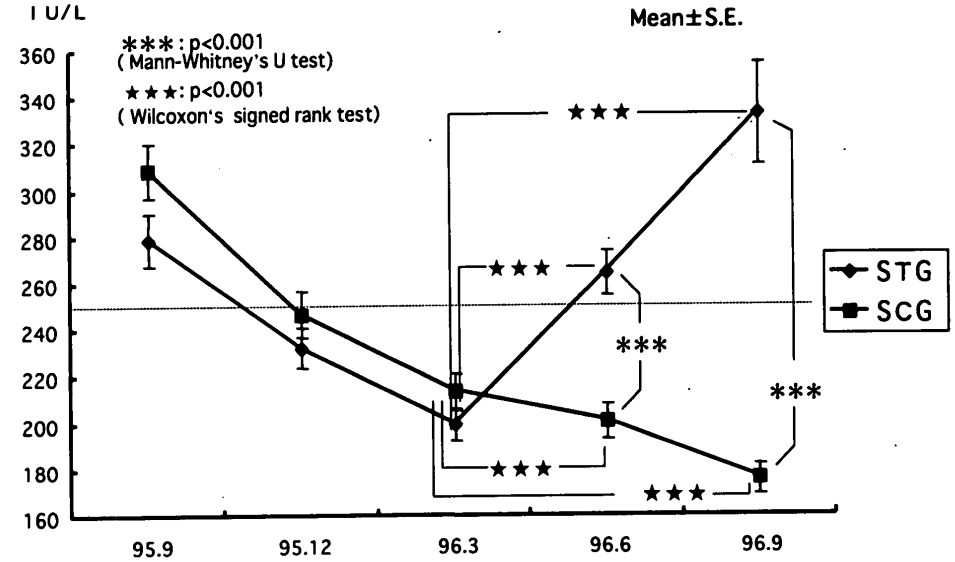

Fig. 7 Liver function (ALP) of the Sho-saiko-to terminated group and continuous treatment group

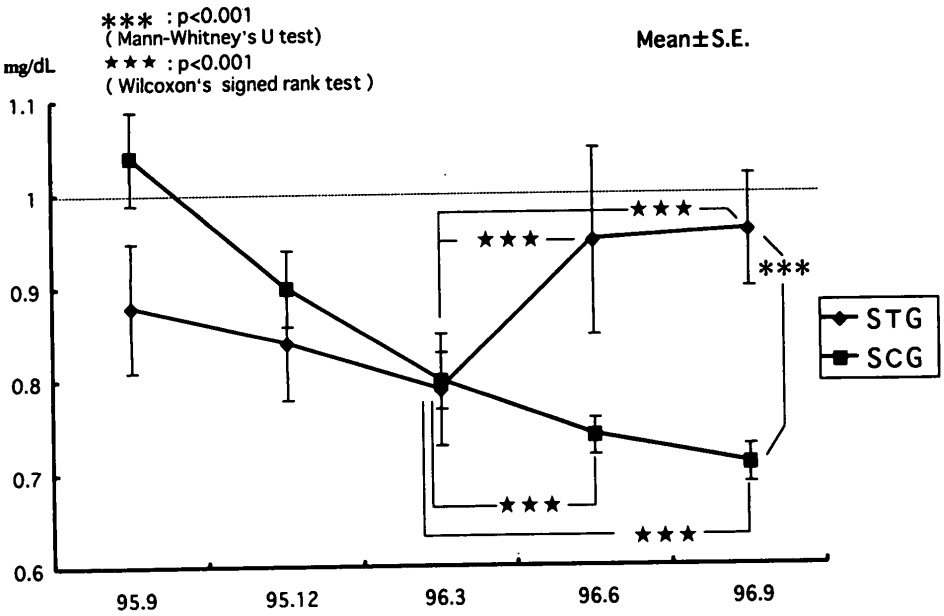

Fig. 8 Liver function (Total bilirubin) of the Sho-saiko-to terminated group and continuous treatment group

The same kinds of changes and the statistical differences were recognized in the serum values of LDH (Fig. 6), ALP (Fig. 7), total bilirubin (Fig. 8), and cholinesterase (Fig. 9) between two groups and between March and June and/or September, 1996. On the other hand, there was no significant difference in serum total cholesterol (Fig. 10), serum total protein (Fig. 11), and serum albumin (Fig. 12), between SCG and STG.

Pneumonia in patients

There was no occurrence of pneumonia or other respiratory diseases among the patients in this study.

Quantitative changes in consumption of therapeutic medicine for hepatic disorders

Figure 13 shows the quantitative changes in prescribed medicines for hepatic disorders in Kitasato University Hospital during the 2 years from March 1995 until March 1997. Eighty-four thousand, one hundred and sixty-nine packages of Sho-saiko-to were prescribed to patients in March, 1995, and this

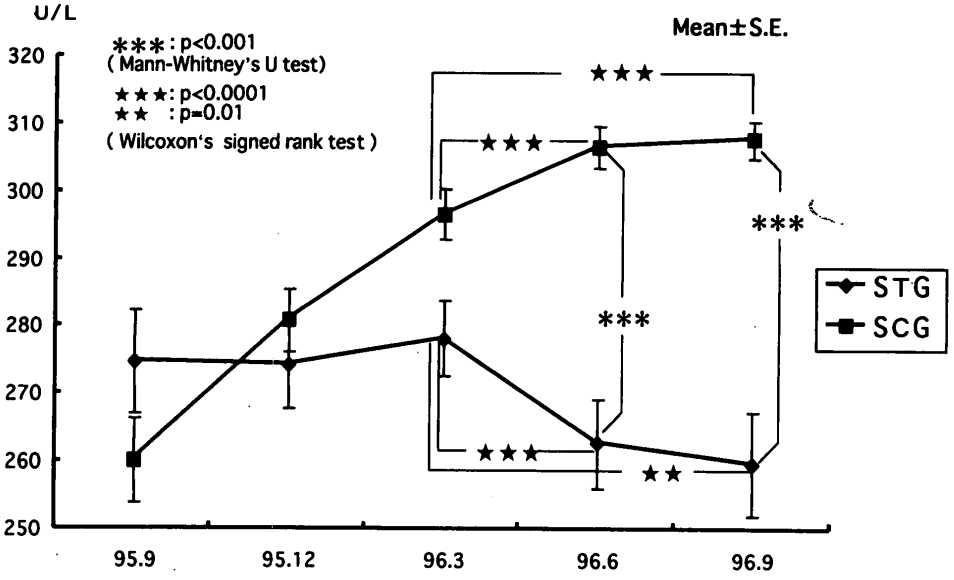

Fig. 9 Liver function (cholinesterase) of the Sho-saiko-to terminated group and continuous treatment group

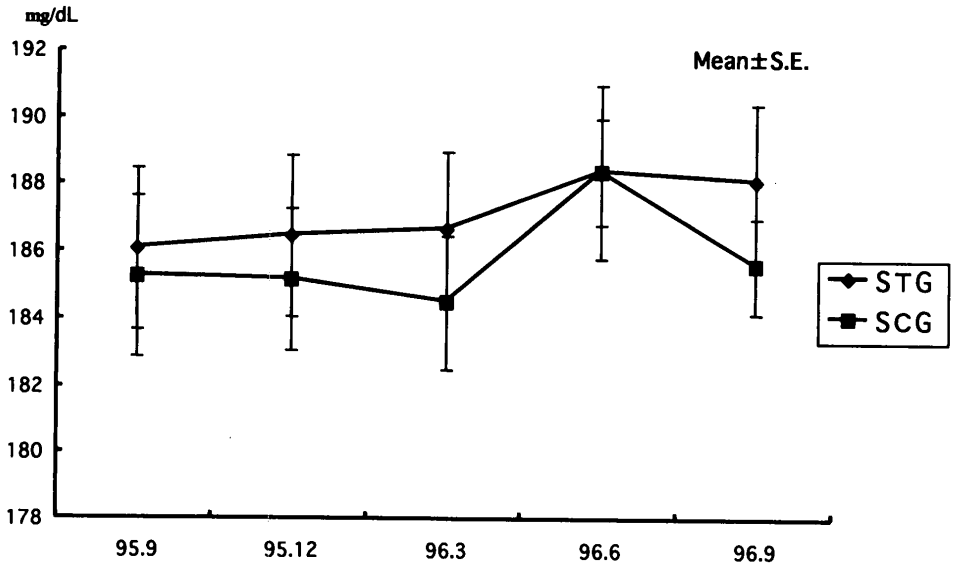

Fig. 10 Liver function (Total cholesterol) of the Sho-saiko-to terminated group and continuous treatment group

volume was the peak amount of Sho-saiko-to prescribed. Sixty thousand, six hundred and sixteen packages was the monthly average number of Sho-saiko-to prescribed from March, 1995 to February, 1996. As described above in "patient background", about three fourths of the patients with hepatic disorders were given Sho-saiko-to. Sho-saiko-to consumption dropped rapidly in March of 1996, when an urgent notice was released, and in April, 1996 26,260 packages of Sho-saiko-to were prescribed, 43.3% of the mean value before February, two months previous. Thereafter, in July, 1996 it had decreased to 18,813 (31.0 %), and this decline continued during the follow-up period. A monthly prescribed number less than 20,000 was first experienced after the UDSI. The monthly average number of prescribed glycyrrhizin tablets

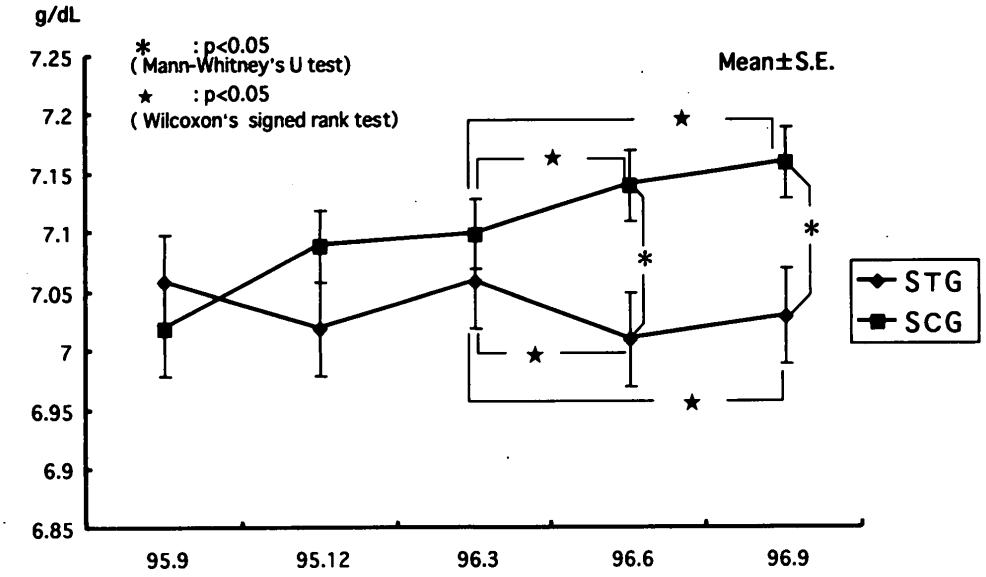

Fig. 11 Liver function (Total protein) of the Sho-saiko-to terminated group and continuous treatment group

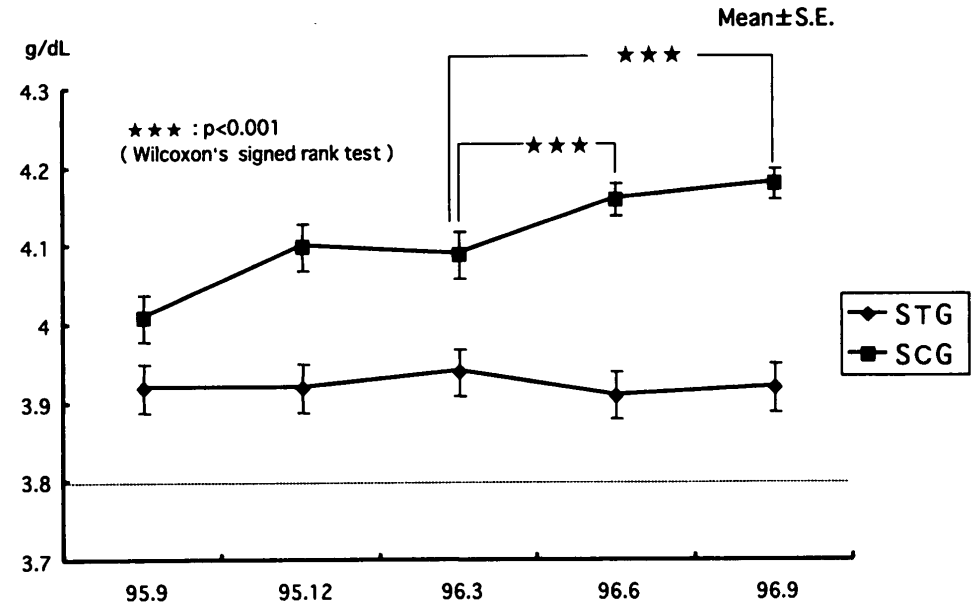

Fig. 12 Liver function (albumin) of the Sho-saiko-to terminated group and continuous treatment group

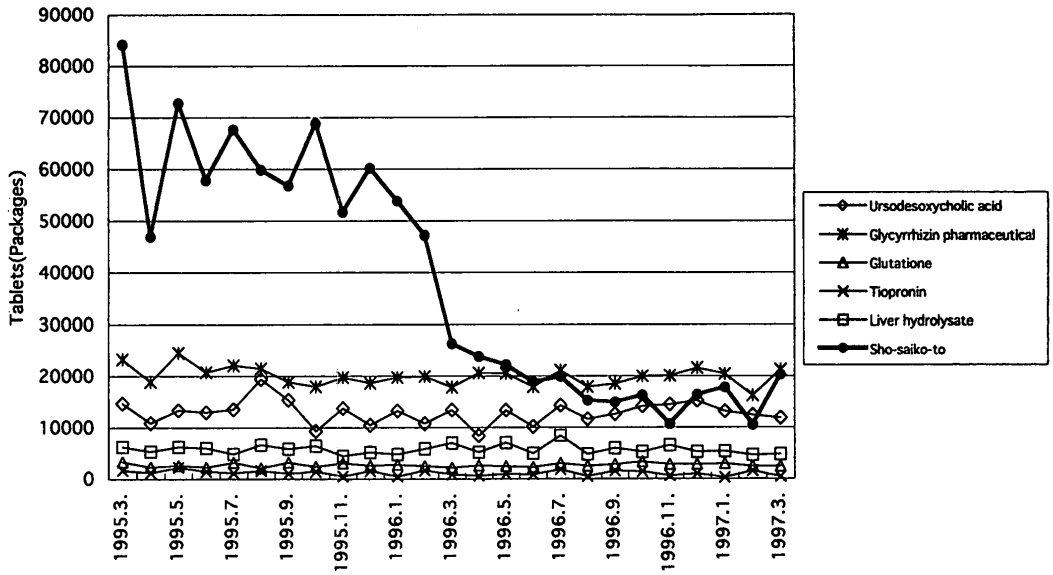

Fig. 13 The transition of leaving shed quantity of liver function improving drugs

(Glycyron, Minophagen, Tokyo) was 20,463 from March, 1995 to February, 1996, while the monthly average number was about 26,500 tablets in the next year, from March, 1996 to February, 1997. Similarly, the monthly average numbers of prescribed tablets of ursodesoxycholic acid (Ursosan, Tokyo Tanabe, Tokyo), liver hydrolysate (Proheparum, Kaken, Tokyo), glutathione (Tathion, Yamanouchi, Tokyo), thiopronine (Thiola, Santen, Osaka) changed from 13,118 to 12,655, from 5,656 to 5,767, from 2,674 to 2,642, from 1,312 to 934 tablets, respectively, from March, 1995 to February, 1996, to the monthly average number in the next year. As shown above, except for Sho-saiko-to, there was no marked change of the usage of medicine for the patients with liver diseases.

Discussion

We have had some experiences in which a noxious adverse effect of a medicine sometimes induces a serious social problem that can be caused by the manner of reporting it and its evaluation methods to the patients and ordinary people, and even to the members belonging to the medical community. In America, the adverse reactions of medicines were reported as being the fourth to sixth cause of the total number of accidental deaths.[10] When a deleterious effect of some drug is suspected, therefore, it is very important to give cautions immediately to the organs of medical services and to the patients and their family members using the suspected drug in order to prevent further incidence and development of such adverse events. However, on the other hand, the clinicians, researchers, officers responsible for drug administration and pharmaceutical companies should make efforts not only to warn but also to clarify the causal relationship between the developed symptoms and the suspected medicine. After determining the causal relationship between the accident and the given drugs, if it is necessary, we should propose ceasing the drug use in some cases, or establishing guidelines and giving suggestions for appropriate applications of the drug to medical doctors and the public. However, when there is no casual relationship involved in the accident, we do not need to give a limitation to medical use of the drug. According to each case, an inadequate cessation of treatment produces the development of the disease and exposes the lives of the patients in treatment to danger.

About 80 published papers concerning interstitial pneumonia have been found to be related to Sho-saiko-to. Unfortunately, we could not find many reports that deeply examined its casual relationship. There are so many arguments about this problem but we can not reach a concrete conclusion. Many doctors who have an interest in and have treated with Kampo medicine and researchers in the field have different opinions. For example, a portion of clinicians think that the

tragedy of Sho-saiko-to may have occurred due to mistakes of the way of administration without suitable Kampo diagnosis, not in accordance with "SHO." Many researchers think that interstitial pneumonitis would be an allergic response and Sato *et al.*[11] reported the immunological characters of Sho-saiko-to-induced pneumonitis. The possibility contaminating idiopathic interstitial pneumonia has not been denied yet.[12]

The clinical role of Sho-saiko-to in these hepatic diseases would lower the blood levels of aminotransferases and other markers of hepatic function, and may suppress the progression of cirrhosis and cancer of liver from the hepatitis. The present results clearly showed that the removal of Sho-saiko-to from the prescriptions resulted in the deterioration of hepatic function. This effect was observed both in cases of Sho-saiko-to single use and combination therapy with other agents for the treatment of hepatic disorders. Especially over ninety percent of the subjects of this study were treated by Sho-saiko-to only before the declaration of the report in March, 1996. It is said that AST and ALT in serum indicates some kind of destruction of hepatic cells but not necessarily reflect all hepatic functions. However, these aminotransferases are the most important markers for hepatic function and the clinical efficacy of Sho-saiko-to would be reconfirmed as a useful and important therapeutic drug for hepatic diseases since the termination of Sho-saiko-to prescription caused a rapid increase in the serum levels of AST and ALT. The clinical efficacy and usefulness of Sho-saiko-to have become clear. So, this important tool for treatment of hepatic disorders should be protected by its adequate use. Recently, the guidelines for Sho-saiko-to treatment in patients with chronic hepatitis C was presented.[13] The appropriate and active treatment should be promoted under these guidelines.

Generally, those who concern themselves with this matter ought to abstain from dispensing information of adverse reaction, to avoid causing anxiety to patients. Especially, there is the historical background in the field of Kampo medicine that more attention is paid to individual case studies and, as a result, the epidemiological approach has been weak until now. Therefore, epidemiological researches on the efficacies and adverse responses should be done actively and evidence-based Kampo should be established on this knowledge after detailed follow up studies on causal relationships with drug usage and frequencies of adverse reactions based on scientific methods. In addition, there was no such case among other Kampo medicines in which such a large scale sudden termination of the administration has occured and it is reporting the rare epidemiological follow-up study.

The follow-up study of the patients who restarted the Sho-saiko-to therapy because of the increases of aminotransferase activities in blood after the stop of the Sho-saiko-to treatment in March, 1996 is now continuing. To avoid a possible social loss due to worsening hepatic functions, it is very important to conduct studies to obtain more accurate information on Sho-saiko-to by pharmacoepidemiological means.

Conclusion

The clinical effectiveness of Sho-saiko-to based on 609 hepatitis patients was studied by pharmacoepidemiological methods. In the cases of patients who suddenly stopped the Sho-saiko-to therapy, the increases in serum aminotransferase activities and other markers were observed. These results showed the usefulness of Sho-saiko-to for maintaining the hepatic functions. The release of some information on the drug adverse reaction needs a well-controlled balance between its usefulness and safety. On the other hand, the detailed evidence based on precise scientific investigation about a causal relationship between the ingestion and frequencies of a crisis should be collected extensively.

A part of this study was reported orally at the 49th Annual Meeting of Japanese Society of Oriental Medicine held in 1998.[14]

和文抄録

肝機能に対する小柴胡湯の影響を薬剤疫学の手法を応用して検討した。対象は1995年9月から1996年9月までの間に北里大学病院を継続受診し，小柴胡湯を含む内服薬で薬物療法を受けていた全外来患者609名とした。そのうち，1996年3月の時点で小柴胡湯のみを中止し，

他の治療薬を継続服用した315名を小柴胡湯服用中止群とした。また，調査期間中，小柴胡湯による治療を継続していた294名を小柴胡湯服用継続群として肝機能の変動を観察した。その結果，小柴胡湯服用継続群は，AST，ALTなどトランスアミナーゼ値は良好にコントロールされていたが，小柴胡湯服用中止群は中止後から徐々に肝機能が悪化する傾向が観察された。γ-GTP，LDH，ALP，総ビリルビン，コリンエステラーゼの各値も同様の傾向を示した。また，総コレステロール，アルブミン，総蛋白の各値に関しては大きな変動が観察されなかった。肺炎などの重篤な副作用は今回の調査においては両群とも観察されなかった。間質性肺炎は小柴胡湯の有害作用として位置づけ常に注意を払うと同時に，単にノンコンプライアンスを助長するような情報提供は慎むべきであると考えられた。さらに，今後は発症の頻度など，詳細な情報に基づいたフォローアップが必要であると考えられた。特に，肝機能悪化に伴う社会的損失や医療費の増加を抑制する意味でも，薬剤疫学を応用した小柴胡湯に関する医薬品情報は重要であると考えられた。

References

1) Hirayama, C., Okumura, S., Tanikawa, K., *et al.*: A multicenter randomized controlled clinical trial of Sho-saiko-to in chronic active hepatitis. *Gastroenterol. Jpn.* **24**, 715-719, 1989.

2) Hirayama, C., Okumura, S., Tanikawa, K., *et al.*: A multicenter randomized controlled clinical trial of Sho-saiko-to in chronic active hepatitis. Analysis of serum enzyme activities. *KAN·TAN·SUI.* **20**, 751-759, 1990.

3) Hirayama, C., Okumura, S., Tanikawa, K., *et al.*: A multicenter randomized controlled clinical trial of Sho-saiko-to in chronic active hepatitis. *KAN・TAN・SUI.* **25**, 551-558, 1992.

4) Oka, H., Yamamoto, S., Kuroki,T., *et al.*: Prospective Study of Chemoprevention of Hepatocellular Carcinoma with Sho-saiko-to(TJ-9). *CANCER.* **76**, 743-749, 1995.

5) Oka, H., Yamamoto, S.: Controlled prospective study of prevention of hepatocellular carcinoma in patients with cirrhosis of the liver. *Digestive Medicine.* **15**, 71-78, 1991.

6) Tsukiyama, K., Tasaka, Y., Nakajima, M., *et al.*: A Case of Pneumonitis due to Sho-saiko-to. *Jpn J Thor Dis.* **27**, 1556-1561, 1989.

7) The Ministry of Health and Welfare: Sho-saiko-to to kanshitsusei-haien (小柴胡湯と間質性肺炎). *Information on Adverse Reactions to Drug.* **107**, 7-8, 1991. (in Japanese)

8) The Ministry of Health and Welfare: Interferon-α seizai oyobi Sho-saiko-to to kanshitsusei-haien (インターフェロン-α製剤および小柴胡湯と間質性肺炎). *Information on Adverse Reactions to Drug.* **118**, 2-5, 1993. (in Japanese)

9) The Ministry of Health and Welfare: Sho-saiko-to no touyo ni yoru jutoku na fukusayou「kanshitsusei-haien」ni tsuite (小柴胡湯の投与による重篤な副作用「間質性肺炎」について). *Information on Adverse Reactions to Drug.* **137**, 8-10, 1996. (in Japanese)

10) Lazarou, J., B.H. Pomeranz, P.N. Corey: Incidence of Adverse Drug Reactions in Hospitalized Patients. A Metaanalysis of Prospective Studies. *JAMA* **279**, 1200-1205, 1998.

11) Sato, A., Toyoshima, M., Kondo, A., *et al.*: Pneumonitis Induced by the Herbal Medicine Sho-saiko-to in Japan. *Jpn J Thor Dis.* **35**, 391-395, 1997.

12) Tashiro, S.: Sho-saiko-to to Kanshitsusei-haien no Kanren ni kansuru Yakurigaku・Ekigaku karano Kentou (小柴胡湯と間質性肺炎の関連に関する薬理学・疫学からの検討). *Jpn J Orient Med.* **49**, 371-381, 1998. (in Japanese)

13) Suzuki, H., Kumada, H., Sato, A., *et al.*: Guidelines of Sho-saiko-to/Xiao-Chaihu-Tang treatment in patients with chronic hepatitis C. *Journal of Traditional Medicines.* **17**, 95-100, 2000.

14) Akase, T., Shimada, S., Tashiro, S.: Evaluation of Efficacy of Kampo Medicines by Pharmacoepidemiological Method: Efficacy of Sho-saiko-to in the Patient with Liver Dysfunction. *Jpn J Orient Med.* suppl **48**, 120, 1998.