

Effect of Kampo treatment on chronic viral hepatitis on the basis of traditional diagnosis

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Abstract

We investigated the effect of Kampo treatment on 47 patients with chronic viral hepatitis on the basis of traditional diagnosis. The number of patients with hepatitis B and C were 8 and 39, respectively. An improvement in serum alanine aminotransferase (ALT) was observed in 75 % of hepatitis B patients and 44 % of hepatitis C patients after six months of the treatment. Symptoms such as easy fatigability and general malaise were brought under control in 90 % of the patients. But liver dysfunction still affected many hepatitis C patients in spite of improvement in symptoms. Comparing the prognosis of 18 hepatitis C patients treated for more than 3 years with reports on the natural course of the disease following a mean 8.8 years after their first visits, the rate of liver cirrhosis was lower, but the rate of hepatocellular carcinoma and the rate of normalization of liver function were similar. Among the major prescriptions used in this investigation was one that included Bupleuri Radix. Many hepatitis C patients showed a good initial response, but their condition later changed to one indicating prescriptions corresponding to Ki deficiency with progression of liver dysfunction. These two kinds of prescriptions could display their effectiveness at different stages. Among additional prescriptions to the main ones, those containing Artemisiae Capillari Spica exhibited the greatest effect. These findings were thought to be important for the design of a prospective control study while making the best use of traditional medicine.

Key words Chronic viral hepatitis, Prescriptions containing Bupleuri Radix, Prescriptions containing Artemisiae Capillari Spica, Prescriptions corresponding to Ki deficiency, Prescriptions corresponding to Oketsu syndrome.

Abbreviations ALT, Alanine aminotransferase; PB, Prescriptions containing Bupleuri Radix, 柴胡剂; PA, Prescriptions containing Artemisiae Capillari Spica, 茵陈蒿剂; PK, Prescriptions corresponding to Ki deficiency, 補気剂; PO, Prescriptions corresponding to Oketsu syndrome, 駆瘀血剂.

Introduction

Recently, interferon treatment for chronic viral hepatitis has achieved significant success, but at the same time limitations of its effect and some adverse reactions have become apparent. Kampo medicines are now being viewed as hopeful agents in the treatment of this disease.

Although Kampo medicines have been considered to be most effective when used on the basis of traditional diagnosis ("Sho"), reports on this disease based on large patient populations have been rare.^{1,2)} The complexity of the traditional diagnostic method can be expected to be simplified by Western modern medicine, but it is still difficult especially with this disease because traditional medicine originally has no concept of chronic hepatitis. To perform a control

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study with good use of "Sho", more information about its relation with this disease will be required. The aim of this study is to investigate the Kampo prescriptions to be used on the basis of traditional diagnosis, their effect on patients' liver dysfunction, and to clarify some parts of "Sho" in regard to this disease in a retrospective manner.

Subjects and Methods

Subjects : Eight patients with chronic hepatitis B and 39 patients with hepatitis C were enrolled in this study. They visited our hospital from October 1979 to March 1996 and were administered Kampo medicines for more than six months, based on the principles of traditional diagnosis.

The 8 hepatitis B patients consisted of 3 males and 5 females, aged 44.9 ± 10.2 years (mean \pm S.D.), and their treatment period was 4.5 ± 4.6 years. The 39 hepatitis C patients consisted of 20 males and 19 females, aged 56.1 ± 12.2 years, with a treatment period of 4.8 ± 4.7 years. Three hepatitis B patients and 6 hepatitis C patients were intolerant to interfer-

on. Regular injections of a drug containing Glycyrrhizin to one hepatitis B patient and two hepatitis C patients were continued even after the administration of Kampo medicines, but no additional treatment with Western medicines was done within six months after the treatment. Eighteen of the hepatitis C patients had histories of blood transfusion.

Protocol of management : The prescriptions adopted in this study were selected according to traditional diagnosis based on the important points listed in Table I.³⁾ Medicinal plants consisting of these prescriptions are shown in Table II.

Assessment of the effect : Assessment of the effect was performed in December 1996, retrospectively. Thirty-three patients had continued to attend our hospital, and 14 patients dropped out during the course of treatment. Evaluation of these discontinued 14 patients, 5 hepatitis B and 9 hepatitis C, was made mainly based on progress notes, as well as partly through questionnaires or by telephone. The method for measuring alanine aminotransferase (ALT) was changed from the Karmen method to the method recommended by JSCC in April 1994, and the figures

Table I Characteristic signs and symptoms indicating each prescription

1) Prescriptions containing Bupleuri Radix	
Sho-saiko-to	thoraco-costal distress, a red tongue with thick fur and sticky saliva, partly anorexia and shoulder stiffness are common in this group
Dai-saiko-to	constipation, tension of abdominal rectus muscle
Saiko-ka-ryukotsu-borei-to	insomnia, palpitation, mental instability
Shigyaku-san	cooling of extremities, tension of abdominal rectus muscle
Saiko-keishi-to	easy to sweat, tension of abdominal rectus muscle
Saiko-keishi-kankyo-to	weak constitution, thirsty, cold feet, sweating of the head and neck
Oren-gedoku-to	feeling of uprising heat, red face, restlessness, insomnia, irritability, tendency for hemorrhage, pruritus
2) Prescriptions corresponding to Ki deficiency	
Hochu-ekki-to	general fatigue, lack of will power, easy fatigability, sleepiness during the day, loss of appetite, edema of tongue, weak pulse of the radial artery and organ ptosis
3) Prescriptions corresponding to Oketsu syndrome	
Keishi-bukuryo-gan	dark-rimmed eyes, livid gingiva and tongue, resistance tender on pressure of the para-umbilical region, hemorrhoids and dysmenorrhea are common in this group, feeling of uprising heat and cooling of the legs, no constipation
Toki-shakuyaku-san	pale face, dizziness and cooling of the extremities
Kami-shoyo-san	marked fatigue, restlessness, fear, insomnia, irritability, sweating, headache, dizziness
4) Prescriptions containing Artemisiae Capillari Spica	
Inchinko-to	constipation, urticaria, jaundice, dry mouth and a feeling of fullness in the upper abdomen

Table II Medicinal plants for Kampo prescription for chronic hepatitis

	BR	SR	GIR	PR	ZR	ZF	PT	CC	H	GiR	RR	AtR	AnR	others
Dai-saiko-to	○	○		○	○	○	○				○			AFI
Saiko-ka-ryukotsu-borei-to	○	○			○	○	○	○	○	○	○			OT FOM
Shigyaku-san	○		○	○										AFI
Sho-saiko-to	○	○	○		○	○	○			○				
Saiko-keishi-to	○	○	○	○	○	○	○	○		○				
Saiko-keishi-kankyo-to	○	○	○					○						OT ZSR TR
Oren-gedoku-to	○	○												CoR PC FF
Hochu-ekki-to	○		○			○				○		○	○	ZSR AsR ANP CiR
Keishi-bukuryo-gan				○				○	○					MC PS
Kami-shoyo-san	○		○	○	○				○			○	○	MC GF MH
Toki-shakuyaku-san				○					○			○	○	CnR AIR
Inchinko-to											○			ACS GF

(Abbreviations) Artemisiae Capillari Spica, 茵陈蒿, ACS; Aurantii Fructus Immaturus, 枳实, AFI; Aurantii Nobilis Pericarpium, 陈皮, ANP; Alismatis Rhizoma, 泽泻, AIR; Angelicae Radix, 当归, AnR; Atractylodis Rhizoma, 白朮, AtR; Astragali Radix, 黄耆, AsR; Bupleuri Radix, 柴胡, BR; Cinnamomi Cortex, 桂枝, CC; Cimicifugae Rhizoma, 升麻, CiR; Cnidii Rhizoma, 川芎, CnR; Coptidis Rhizoma, 黄连, CoR; Forsythiae Fructus, 连翘, FF; Fossilia Ossus Mastodi, 龟骨, FOM; Gardeniae Fructus, 山梔子, GF; Ginseng Radix, 人参, GiR; Glycyrrhizae Radix, 甘草, GIR; Hoelen, 茯苓, H; Moutan Cortex, 牡丹皮, MC; Menthae Herba, 薄荷, MH; Ostreae Testa, 牡蛎, OT; Phellodendri Cortex, 黄柏, PC; Paeoniae Radix, 芍药, PR; Persicae Semen, 桃仁, PS; Rhei Rhizoma, 大黄, RR; Scutellariae Radix, 黄芩, SR; Trichosanthis Radix, 栝楼根, TR; Zizyphi Fructus, 大枣, ZF; Zingiberis Rhizoma, 生姜, ZR; Zingiberis Siccatur Rhizoma, 乾姜, ZSR

after the change were divided by the index 1.44.

I Short-term effect

1) Changes of serum ALT levels

The effect of Kampo medicines was estimated by the changes of serum ALT levels after six months of administration; cases with ALT decrease over 50 % were judged as "marked improvement", cases with ALT decrease from 21 % to 50 % as "mild improvement", cases with ALT decrease within 20 % or fluctuating within normal range as "unchanged", and cases with ALT increase over 20 % as "aggravation".

2) Investigation of Kampo medicines administered on the basis of traditional diagnosis

We investigated Kampo medicines according to traditional diagnosis in the initial six months of their use by classification into prescriptions containing Bupleuri Radix (PB), prescriptions corresponding to Ki deficiency (PK), prescriptions corresponding to Oketsu syndrome (PO) and prescriptions containing Artemisiae Capillari Spica (PA).

3) Effect on symptoms indicating Ki deficiency.

We investigated the change of symptoms indicating Ki deficiency such as general malaise and easy fatigability during the initial six months by analysis of progress notes and questionnaires.

II Long-term effect

1) Hepatitis B

We estimated the effect on hepatitis B patients by normalization of serum ALT and seroconversion.

2) Hepatitis C

We analyzed the change of serum ALT of hepatitis C patients during the initial three years of treatment at half-year intervals. The Friedman test was used for statistical analysis. We also investigated the stable period in 18 patients treated for more than three years with Kampo medicine, to determine how long our treatment had kept their liver function stable, and we analyzed the prescriptions used.

Results

I Short-term effect

1) Changes of serum ALT levels (Fig. 1)

According to the criteria, among the 8 hepatitis B patients, marked improvement was seen in 5 (63 %), and mild improvement, unchanged and aggravation in one each. On the other hand, among the 39 hepatitis C patients, marked improvement was seen in 7 (18 %), mild improvement in 10 (26 %), unchanged in 12 (31 %) and aggravation in 10 (26 %). Therefore, the

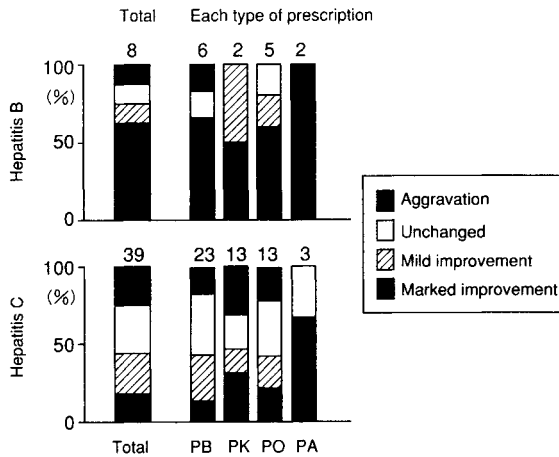


Fig. 1 The effect of Kampo medicines for patients with chronic hepatitis according to changes in ALT levels measured after 6 months of treatment. The effect on hepatitis B in the upper bar graph and on hepatitis C in the lower. Figures above the columns indicate the number of patients for each prescription.

short-term effect was superior in hepatitis B compared to hepatitis C.

2) Investigation of Kampo medicines administered on the basis of traditional diagnosis

For the 8 hepatitis B patients, 6 PB and 2 PK were administered. We used 23 PB and 13 PK in the 39 hepatitis C patients, and we excluded the 3 cases because their prescriptions were changed within the initial 6 months of treatment according to traditional

diagnosis. PB was used more than PK in both types of hepatitis.

The contents of PB were somewhat different between the two types of hepatitis. In hepatitis B patients Saiko-keishi-to was administered to 3 of the 6, and in hepatitis C patients Saiko-keishi-kankyo-to was given to 9 of the 39, Saiko-keishi-to to 5, Saiko-ka-ryukotsu-borei-to to 3 and Shigyaku-san to 3. The contents of PK revealed that Hochu-ekki-to was given to 13 of the total 15.

PO and PA were always used together with PB or PK. Keishi-bukuryo-gan was the most frequently used PO, 13 of the 18. All PA consisted of Inchin-ko-to, and marked improvement was attained in 4 of the 5 patients.

3) Effect on symptoms indicating for Ki deficiency.

Five hepatitis B patients (63 %) and 31 hepatitis C patients (79 %) had symptoms indicating Ki deficiency, such as general malaise and easy fatigability. There was no difference in the effect on ALT levels between with or without the symptoms. Four hepatitis B (80 %) and 27 hepatitis C (87 %) showed improved symptoms.

II Long-term effect

1) Patients with hepatitis B

Three of the 5 patients with positive HBeAg had seroconversion, which was recognized at six months, two years and four months, and two years and ten months of Kampo treatment, respectively (Fig. 2).

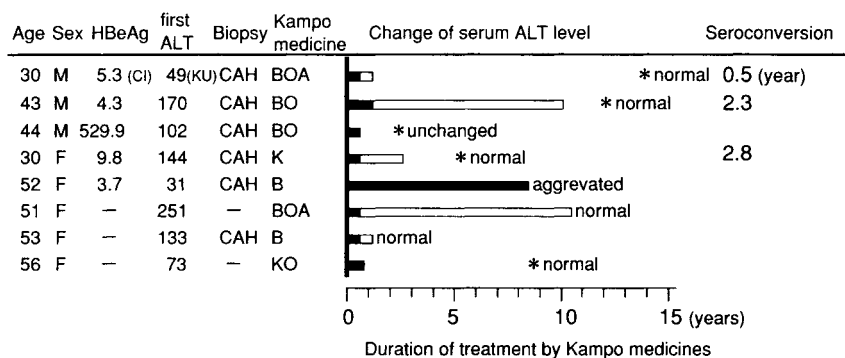


Fig. 2 Long-term results of patients with chronic hepatitis B treated by Kampo medicines for more than half a year

Characteristics and changes of serum ALT levels of 8 patients with hepatitis B treated with Kampo medicines for more than a half a year. The Kampo medicines were classified into four types of prescriptions: B, Bupleuri Radix; K, Ki deficiency; O, Oketsu syndrome; A, Artemisiae Capillari Spica. The length of the columns shows the treatment duration. The open and closed columns indicate normal and abnormal ALT levels, respectively. Asterisks indicate the time point of this investigation.

One patient discontinued our treatment and the other one had progressed to liver cirrhosis in spite of continuing treatment. The liver dysfunction of the three patients with negative HBeAg improved within one year after beginning treatment.

2) Patients with hepatitis C

We investigated the liver function of 18 patients throughout the course of receiving treatment for more

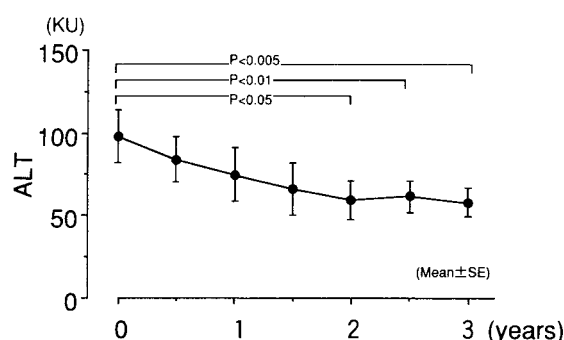


Fig. 3 Serum ALT level in patients with hepatitis C with more than three years of treatment with Kampo medicines

This analysis was done with 16 of 18 patients, because two cases were lacking one or two points of serum ALT. Statistical analysis was performed by the Friedman test.

than three years. The serum ALT levels of 16 of the 18 patients were measured every half year up to three years after the start of treatment (Fig. 3). It was 98.1 ± 16.0 KU (mean \pm S.E.) before treatment began and gradually decreased to 59.4 ± 11.6 KU after 2.0 years, 61.6 ± 10.0 KU after 2.5 years and 58.2 ± 8.7 KU after 3.0 years. The changes were statistically significant from two years after the beginning of treatment.

In addition, we investigated stable periods of the 18 patients; their ALT levels stayed below double the value of the normal upper limit, platelet counts were normal, and there was no abnormality of liver shape (Fig. 4). We could calculate stable periods in 14 patients (No. 1~14), but four patients (No. 15~18) were unstable throughout the study.

The unstable cases were considered to have more severe inflammation because their initial ALT levels were 150 ± 80 KU (mean \pm S.D.), higher than 78 ± 44 KU of the cases who had obtained stable periods. Three unstable cases discontinued coming to our hospital and two of them died later. The stable period began from 1.3 ± 1.8 years following the start of treatment and continued for 6.0 ± 3.8 years.

At the end of this investigation, there were 3

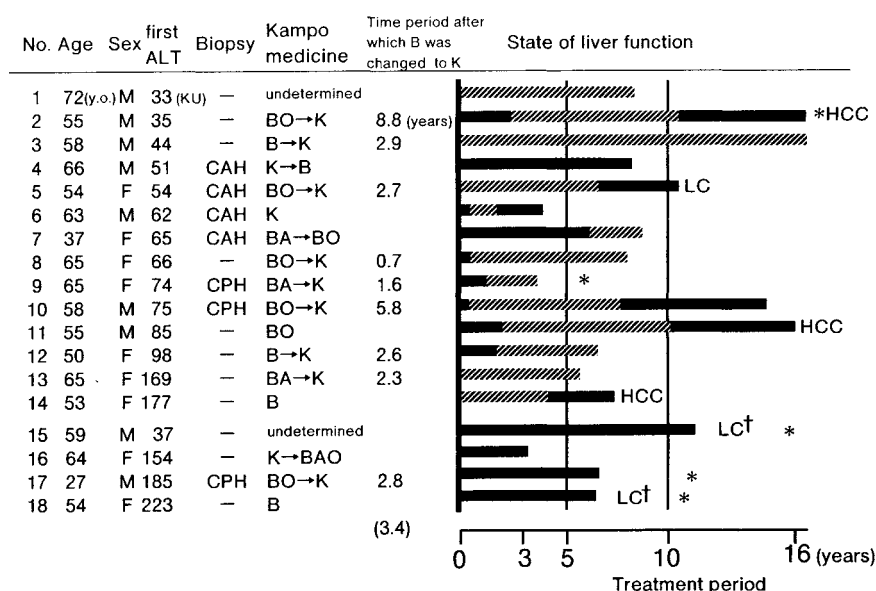


Fig. 4 Long-term results of 18 patients with hepatitis C following more than three years of Kampo treatment

Characteristics and liver functions of the patients. The mean treatment period was 8.8 ± 4.3 years (mean \pm S.D.). The Kampo medicines were classified into four types of prescriptions: B, Bupleuri Radix; K, Ki deficiency; O, Oketsu syndrome; A, Artemisiae Capillari Spica. The hatched columns indicate stable liver function and the closed columns indicate unstable liver function. Asterisks indicate the time point of this investigation. LC and HCC mean liver cirrhosis and hepatocellular carcinoma, respectively. † indicates death.

patients with liver cirrhosis (2 had already died) and 3 patients with hepatocellular carcinoma. Patients with stable liver function after 5 years of treatment were 9 of 15 (60 %), 3 of 6 (50 %) at 10 years, and only 1 of 4 (25 %) after more than 10 years.

Analysis of Kampo medicines used for hepatitis C patients showed that 8 of the 18 patients who had initially responded to PB gradually became to respond to PK. This pattern of changing prescriptions was mostly seen in the stable cases. The average period after which PB changed to PK was 3.4 years after the start of treatment.

Discussion

Following the report that interstitial pneumonia was a possible adverse effect of Sho-saiko-to, the safety and effect of the use of Kampo prescriptions for many of the illnesses in modern Western medicine have been discussed.⁴⁾ Recently, the importance of the way of traditional diagnosis ("Sho") in the use of Kampo prescriptions has come to be widely described even in package insert drug information pamphlets of Kampo prescriptions. "Sho" is judged comprehensively by a complex of subjective and objective symptoms at a certain point of illness. The process is generally complicated, but it can be quite simple in some diseases such as Bakumondo-to indicated for dry cough of patients with acute bronchitis. However, in the case of patients with chronic hepatitis, there is no mutually characteristic symptom indicated for the condition in both modern Western medicine and "Sho". We need to accumulate more information about "Sho" in this disease for the purpose of designing a prospective control study while making the best use of traditional medicine.

One new fact was revealed in this study by physicians who treated the patients on the basis of traditional diagnosis, which was that the symptoms for Ki deficiency did not reflect the state of the illness after six months of treatment. There might have been a tendency that they easily estimated the subjective symptoms as the state of the illness in accordance with traditional diagnosis, but this does not seem to hold true for the treatment of patients with hepatitis C. We have to estimate the effect on the symptoms

and the laboratory data separately.

The effect of Kampo medicines mainly used by PB and PO on hepatitis B is already known.^{5,6)} Even in this study, 3 of 5 patients achieved seroconversion within the initial three years of treatment. This result shows, although the number of patients is small, that this rate may exceed the reported 3~5 % per year of the natural rate of seroconversion.⁷⁾

In general, hepatitis C cannot heal naturally, but serum ALT levels of most of our patients after more than two years of treatment, although not reaching normal range, had apparently decreased. Fourteen of the 18 patients (78 %) could get liver function stability for an average period of about six years. There were three patients (17 %) with liver cirrhosis, three patients (17 %) with hepatocellular carcinoma and one patient (6 %) with normalization of liver function after an average period of 8.8 years of treatment. Some reports about the natural course of chronic hepatitis C after the same period indicated cirrhotic rates of 32 % (49 out of 155 ; Inoue *et al.*⁸⁾), 30 % (20 out of 66 ; Nakano *et al.*⁹⁾) and 33 % (32 out of 98 ; Yatsumata *et al.*¹⁰⁾). These figures were much higher than our 17 %, but this comparison may lack in validity because of our small patient population and incomplete follow-up by liver biopsies. Nevertheless, it appears that Kampo prescriptions on the basis of traditional medicine might decrease the cirrhotic rate from chronic hepatitis.

Otherwise, the rates of hepatocellular carcinoma and normalization of liver function were similar to those of the reports of the natural course of chronic viral hepatitis with the same follow-up period.^{8,9,10)} Considering the report by Oka *et al.* that the five-year administration of only Sho-saiko-to prevented the development of hepatocellular carcinoma in cirrhotic patients without HBs antigen,¹¹⁾ we have to recognize that our treatment needs to be improved in order to achieve similar results.

In the present study, many patients responded to PB, but after more than three years of treatment, 8 of the 18 hepatitis C patients gradually changed to respond to PK, becoming less responsive to PB. Considering Yamauchi's report that many patients with liver cirrhosis respond to PK,²⁾ there might be a tendency for patients with hepatitis C to gradually

come to respond to PK before progressing to liver cirrhosis. The favorable effect of PK on hepatitis C was recently reported,^{12,13)} but we might consider that this effect is exhibited mostly at the relatively advanced stage of the disease.

PA remarkably improved liver dysfunction in 4 of 5 patients. It consists simply of *Gardeniae Fructus*, *Artemisiae Capillari Spica* and *Rhei Rhizoma*. Its additive effect with PB or PK is especially noteworthy. Its indication might be broader, as patients who responded to PA did not necessarily have jaundice and itching, said to be the traditional indications for its use. The more frequent use of PA might increase the effect of our treatment of chronic hepatitis.

Conclusions

- 1) We studied the effect of Kampo treatment on chronic viral hepatitis on the basis of traditional diagnosis.
- 2) Subjective symptoms such as general malaise and easy fatigability were improved in most patients after six months of the treatment, but we have to estimate the effects on symptoms and the laboratory data separately, especially in hepatitis C.
- 3) Compared with reports on the natural course, there is a possibility that Kampo prescriptions on the basis of traditional medicine might decrease the cirrhotic rate from chronic hepatitis. However, the rate of hepatocellular carcinoma and normalization of liver function were similar to those of the natural course.
- 4) Many patients responded to PB, but patients with hepatitis C gradually became to respond to PK with the progression of liver dysfunction.
- 5) The additive effect of PA to PB or PK is especially noteworthy, in spite of small number of cases. To use PA frequently might increase the effect of our treatment of chronic hepatitis.

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和文抄録

慢性 B 型および C 型肝炎 47 症例 (B 型 8 例, C 型 39 例) に対する和漢薬随証治療の効果について検討した。治療 6 ヶ月時の血清 ALT 値の改善は B 型 75 %, C 型 44 % であった。易疲労, 倦怠感などの症状は両型とも約 9 割の症例で改善されたが, C 型では症状と検査値の結果が一致しない例が多くみられた。治療期間 3 年以上の 18 例について平均 8.8 年の時点で自然経過報告と比較してみると肝硬変への移行率は少なかったが肝細胞癌の発生頻度と臨床的治癒の率は同等であった。使用方剤は両型ともに柴胡剤が多いが, C 型の証は柴胡剤で始まり肝障害の進行とともに補剤に変化する傾向を認めた。柴胡剤と補剤には使用すべき時期に相違があるように考えられた。また併用方剤としては茵陳蒿剤が最も高い改善効果を有していた。これらの知見は証を活かしたコントロールスタディを企画していく上で重要と考えられた。

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