Incidence of Herb-induced Liver Injury Caused by Kampo Formulae Containing Scutellariae Radix

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Objective: Herb-induced liver injury due to Kampo formulae is a clinically relevant adverse effect, which may be associated with formulae containing Scutellariae Radix. We explored this incident relationship further by surveying outpatients treated with a Kampo formula containing Scutellariae Radix (KFCSR) at our clinic.
Methods: We included patients who had been treated with a novel KFSCR formulation between November 2014 and October 2015. The participants underwent liver injury-related blood tests (examining the aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, gamma-glutamyl transpeptidase, and total bilirubin levels, as well as the percentage of eosinophils in the white blood cell count) before and after treatment to evaluate its efficacy.
Results: In total, 43 of the 363 patients treated during the study period received KFCSRs and 37 underwent blood tests before and after treatment. Liver injury occurred in four patients (10.8%) and all patients recovered quickly after cessation of the formula.
Conclusions: We found that 10.8% of patients treated with KFCSR developed liver injury, which was higher than that reported previously. We believe that herb-induced liver injury should be seriously considered as a risk factor for KFCSRs. Further investigation is warranted to verify these results.

Key words: Kampo, traditional Japanese medicine, herb-induced liver injury, Scutellariae Radix

INTRODUCTION

Ethical Kampo extract formulae were first incorporated into Japan's National Health Insurance Drug List in 1967. Thereafter, the use of Kampo formulae increased throughout the country. Although Kampo formulations are considered safe owing to their long history of use, increased usage by physicians has led to a concerning spike in adverse effects in clinical settings [1, 2]. Pseudoaldosteronism due to Glycyrrhizae Radix [1, 3] and mesenteric phlebosclerosis induced by Gardeniae Fructus are well-known adverse effects of Kampo formulae [4], and several incidents of liver injury resulting from general Kampo formulae have been reported [5]. The Japanese Society of Hepatology analyzed 1,676 cases of herb-induced liver injury between 1997 and 2006 and found that out of the 879 injuries that were caused by one drug, 7.1% were attributed to Kampo formulations [6].

In Japan, Scutellariae Radix has come under increased scrutiny as an herbal medicine that is closely linked to herb-induced liver injury and interstitial pneumonia. Scutellariae Radix (root of *Scutellaria baicalensis* Georgi; "*ogon*" in Japanese) is a crude drug that is the probable cause of herb-induced liver injury by Kampo formulations. Scutellariae Radix is also strongly associated with herb-induced interstitial pneumonia caused by Kampo formulae [7]. Several pharmaco-epidemiological studies have shown that 89% of herb-induced liver injuries and 94% of herb-induced interstitial pneumonia cases are caused by Kampo formulae containing Scutellaria Radix (KFCSR) [8]. A recent study revealed that 86% of herb-induced interstitial pneumonia cases caused by Kampo formulae occur due to KFCSRs [9]. A high incidence of liver injury was similarly noted in a study conducted in Germany, in which 20 of 26 cases of herb-induced liver injury related to the use of herbal medicine of Traditional Chinese Medicine occurred with formulae containing Scutellariae Radix [10].

However, the incidence of liver injury following treatment with a KFCSR has not been examined in detail. The incidence of herb-induced liver injury in post-marketing studies of shosaikoto (*Xiao Chai Hu Tang* in Chinese), which contains Scutellariae Radix, is 0.5%; however, these studies provide incomplete information (e.g., the numbers of blood samples evaluated are not stated) [11]. Itoh *et al.* [12] reported that the incidence of herb-induced liver injury caused by KFCSRs was 1%; however, the number of blood samples evaluated in this study was not reported clearly, which probably biased the true incidence.

Given the shortcomings of the previous research, we conducted a preliminary study to determine the incidence of herb-induced liver injury caused by KFCSRs by evaluating blood samples of patients before and after they underwent treatment over a 1-year period.

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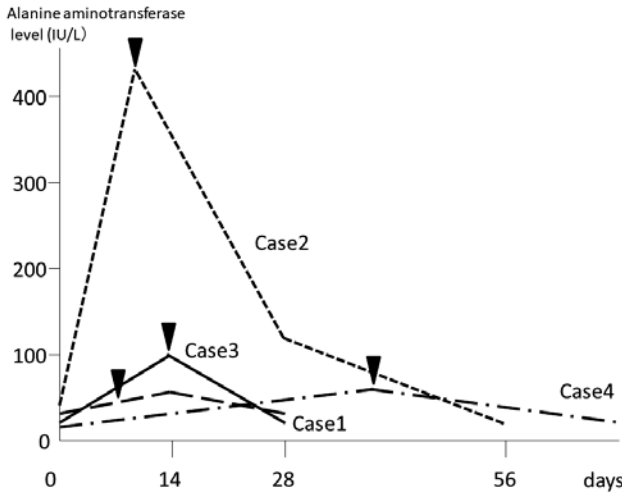

Fig. 1 Changes in alanine aminotransferase levels during liver injury
The downward arrowhead indicates the time when the Scutellariae Radix-containing formulae were discontinued.

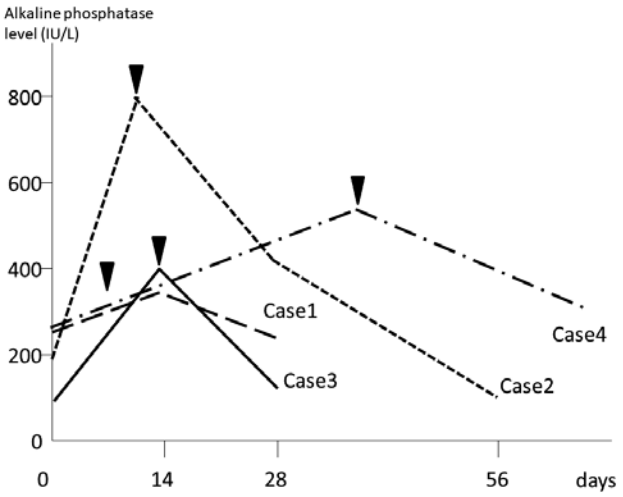

Fig. 2 Changes in alkaline phosphatase levels during liver injury
The downward arrowhead indicates the time when the Scutellariae Radix-containing formulae were discontinued.

MATERIALS AND METHODS

We conducted our study on outpatients who were newly treated with KFCSRs by the first author at a clinic specializing in Kampo medicine at Joetsu general Hospital between November 1, 2014, and October 31, 2015. All patients underwent blood tests to evaluate liver dysfunction [aspartate aminotransferase (AST; normal range, 13–33 U/L), alanine aminotransferase (ALT; normal range, 6–27 U/L), alkaline phosphatase (ALP; normal range, 115–359 U/L), gamma-glutamyl transpeptidase (γGTP; normal range, 10–47 U/L), total bilirubin levels (T-Bil; normal range, 0.1–1.1 mg/dL), and percentage of eosinophils in white blood cell (Eos; normal range, 0–5%)] at two time points (i.e., immediately before starting the KFCSR treatment and at a follow-up visit at 2–6 weeks after treatment). We examined the levels of immunoglobulin M (IgM) hepatitis A virus antibody, hepatitis B surface antigen, hepatitis C virus antibody, and antinuclear antibody and also performed abdominal ultrasonography to exclude the presence of other liver diseases besides herb-induced liver injury, such as viral hepatitis, fatty liver, shock liver, and autoimmune hepatitis.

Patients with genuine hepatic dysfunction were evaluated using the Digestive Disease Week-Japan 2004 workshop Criteria for Diagnosis of drug-induced liver injury (DDWJ2004CD) [13]. Drug-induced liver injury addressed by this criterion is defined as cases of hepatocellular, cholestatic, or combined hepatocellular-cholestatic hepatitis, with ALT levels being two times higher than the normal range or ALP levels being above the upper limit of the normal range. First, we classified liver injury as hepatocellular, cholestatic, or combined hepatocellular-cholestatic, based on the ALT and ALP levels. Second, we calculated a total score from eight items (i.e., period until onset, course, risk factors, presence or absence of a non-drug-related cause, report of past liver injury, eosinophilia, herb-induced lymphocyte stimulation test [DLST] results, and response in cases of incidental administration). A diagnosis of herb-induced liver injury is highly probable if the score is >4 points, probable if the score is 3–4 points, and not probable if it is <3 points. Vis-à-vis non-herb-related causes of liver injury, our diagnostic criteria indicated that category 1 included hepatitis A, hepatitis B, and hepatitis C viral infections, biliary disease, alcoholic liver disease, and ischemic hepatitis (i.e., shock liver), and category 2 included cytomegalovirus and Epstein-Barr virus infections. However, we did not use DLST for diagnosis in this study.

The study design was approved by the Ethics Committee of Joetsu General Hospital (Reference no. 220). The requirement for obtaining informed patient consent was waived due to the retrospective nature of this study. The investigation conforms with the principles outlined in the Declaration of Helsinki.

RESULTS

We treated 363 patients (male to female ratio, 77:286; mean age ± standard deviation, 56.1 ± 17.9 years) during the study period. 43 of the 363 patients received KFCSR treatment, of whom 37 (male to female ratio, 12:25; mean age ± standard deviation, 48.3 ± 17.3 years) underwent blood tests before and after taking the prescription. One patient did not return for a follow-up visit and five patients were unable to have blood drawn after KFCSR administration; thus, we excluded six patients from the study.

We observed liver injury in four of 37 patients (10.8%); all four cases were classified as "probable" according to the DDWJ2004CD. The fluctuations in the ALT and ALP levels in the four patients are presented in Fig. 1 and 2, respectively. A summary of the four patients is presented below.

Patient 1

A 48-year-old man was treated with sanmotsuogonto extract (7.5 mg/day; TJ-9, Tsumura & Co., Tokyo, Japan; *San Wu Huang Qin Tang* in Chinese) for eczema of the hand. The patient's blood test results before sanmotsuogonto administration were as follows: AST, 27 U/L; ALT, 37 U/L; ALP, 259 U/L; γGTP, 88 U/L; T-Bil, 0.5 mg/dL; and Eos, 12.0%. However, the

patient experienced nausea after 7 days of receiving sanmotsuogonto, and stopped taking it. Blood tests conducted on day 14 at other clinic revealed liver dysfunction as follows: AST, 50 U/L(normal range, 13–30 U/L); ALT, 60 U/L(normal range, 10–42 U/L); ALP, 336 U/L(normal range, 106–322 U/L); γGTP, 110 U/L(normal range, 13–64 U/L); T-Bil, 0.4 mg/dL(normal range, 0.4–1.5 mg/dl); and Eos, 5.2%(normal range, 2.0–6.0%). The blood biochemical markers were improved at 3 weeks after discontinuing the formula (i.e., 28 days later) as follows: AST, 26 U/L; ALT, 32 U/L; ALP, 248 U/L; γGTP, 72 U/L; T-Bil, 0.5 mg/dL; and Eos, 7.0%. The patient tested negative for IgM hepatitis A virus antibody, hepatitis B surface antigen, hepatitis C virus antibody, and antinuclear antibody. No abnormal findings were observed on abdominal ultrasonography. We classified the liver injury as cholestatic, with a score of 7 points and a "probable" rating according to the DDWJ2004CD.

Patient 2

A 69-year-old man was treated with orengedokuto extract (7.5 mg/day; TJ-15, Tsumura & Co.; *Huang Lian Jie Du Tang* in Chinese) for urticaria. The patient's blood test results before orengedokuto administration were as follows: AST, 35 U/L; ALT, 45 U/L; ALP, 195 U/L; γGTP, 93 U/L; T-Bil, 0.9 mg/dL; and Eos, 11.9%. However, blood tests conducted at 11 days after the initiation of orengedokuto administration provided the following evidence of liver dysfunction: AST, 382 U/L; ALT, 421 U/L; ALP, 785 U/L; γGTP, 519 U/L; T-Bil, 2.4 mg/dL; and Eos, 14.4%. Therefore, we discontinued the formula. The blood test results conducted 28 days later (i.e., at 17 days after stopping the formula, showed improvement in liver function) were as follows: AST, 47 U/L; ALT, 111 U/L; ALP, 408 U/L; γGTP, 295 U/L; T-Bil, 1.2 mg/dL; and Eos 7.6%. The patient tested negative for IgM hepatitis A virus antibody, hepatitis B surface antigen, hepatitis C virus antibody, and antinuclear antibody. No abnormal findings were observed on abdominal ultrasonography. We classified liver injury as combined hepatocellular-cholestatic, with a score of 8 points and a "probable" rating according to the DDWJ2004CD.

Patient 3

A 72-year-old woman was treated with unseiin extract (7.5 mg/day; TJ-106, Tsumura & Co.; *Wen Qing Yin* in Chinese) for eczema of the face. The patient's blood test results before unseiin administration were as follows: AST, 31 U/L; ALT, 21 U/L; ALP, 145 U/L; γGTP, 66 U/L T-Bil, 0.6 mg/dL; and Eos, 7.7%. However, at 2 weeks after starting the course of unseiin, blood test results revealed liver dysfunction as follows: AST, 129 U/L; ALT, 96 U/L; ALP, 388 U/L; γGTP, 294 U/L; T-Bil, 0.5 mg/dL; and Eos, 7.1%. Therefore, we discontinued the formula. The results of the blood test improved after 28 days (i.e., at 14 days after stopping the formula: AST. 23 U/L; ALT, 20 U/L; ALP, 153 U/L; γGTP, 130 U/L; T-Bil, 0.7 mg/dL; and Eos, 8.2%). The patient tested negative for IgM hepatitis A virus antibody, hepatitis B surface antigen, hepatitis C virus antibody, and antinuclear antibody. No abnormal findings were observed on abdominal ultrasonography. We classified the liver injury as combined hepatocellular-cholestatic, with a score of 8 points and a "probable" rating according to the DDWJ2004CD.

Patient 4

A 70-year-old woman was treated with shin'iseihaito extract (7.5 mg/day; TJ-104, Tsumura & Co.; *Xin Yi Qing Fei Tang* in Chinese) for sinusitis. The patient's blood test results before shin'iseihaito administration were as follows: AST, 12 U/L; ALT, 16 U/L; ALP, 257 U/L; γGTP, 14 U/L; T-Bil, 0.6 mg/dL; and Eos, 5.4%. However, blood tests conducted at 38 days after initiating medication containing shin'iseihaito revealed liver dysfunction as follows: AST, 20 U/L; ALT, 52 U/L; ALP, 490 U/L; γGTP, 335 U/L; T-Bil, 0.5 mg/dL; and Eos, 4.7%; this prompted us to discontinue the formula. After 66 days (i.e., 28 days after stopping the formula), the blood test results showed improvement as follows: AST, 14 U/L; ALT, 15 U/L; ALP, 275 U/L; γGTP, 92 U/L; T-Bil, 0.5 mg/dL; and Eos, 1.1%. The patient tested negative for IgM hepatitis A virus antibody, hepatitis B surface antigen, hepatitis C virus antibody, and antinuclear antibody. No abnormal findings were observed on abdominal ultrasonography. We classified liver injury as combined-cholestatic, with a score of 6 points and a "probable" rating according to the DDWJ2004CD.

DISCUSSION

The incidence of herb-induced liver injury caused by Kampo formulae reported by previous retrospective studies is similar: one facility reported liver injury in 15 out of 14,616 patients (0.10%) and another one reported the same in 21 of 20,271 patients (0.10%) [14, 15]. Outside Japan, 26 (0.12%) of 21,470 patients treated with Chinese herbal medicines in Germany were reported to have developed liver damage with ALT levels exceeding five times the upper normal range [10]. A previous study reported that 6 (0.6%) out of 1,001 inpatients (360 men and 641 women) who were treated with Korean herbal medicine at 10 tertiary hospitals across Korea developed liver damage [16]. These statistics are probably accurate and provide reasonable evidence that Kampo or traditional herbal formulae can be used relatively safely. However, it is necessary to evaluate the incidence of herb-induced liver injury in KFCSRs separately, which is known to be a frequent cause of liver injury.

As aforementioned, Itoh *et al.* reported a 1.0% incidence of liver injury (13 of 1,328 cases) following treatment with a KFCSR [12]. However, this study did not state the number of blood tests performed, which may have caused the researchers to overlook liver dysfunction; therefore, it is possible that the reported incidence was not accurate. In 2017, Mantani *et al.* reported that 19 (1.2%) of 1,547 patients who received KFCSR developed herb-induced liver injury [17]. The incidence of liver injury in Ito *et al.*'s [12] and Mantani *et al.*'s studies [17] is consistent at approximately 1%. However, the actual incidence of liver injury may be different as Mantani *et al.*'s study [17] was marred by several instances of patient drop-out (334 patients) and non-collection of blood samples (549 patients). In the present study, we examined 37 of 43 patients before and after receiving KFCSRs, and four of them

(10.8%) developed "probable" drug-induced liver injury (per the DDWJ2004CD). This proportion is extremely high and surprising, especially when compared to the above-mentioned studies. However, we refrained from generalizing our results immediately, as the reasons for the high incidence of herb-induced liver injury observed in this study are numerous.

First, the number of cases included in this study was very small, and the data are possibly biased. Second, we assessed patients who attended an outpatient clinic specializing in Kampo medicine. Some of these patients visit Kampo practitioners because they are allergic to modern Western drugs, fearful of their side effects, or wish to avoid them for moral reasons. This may result in a false higher incidence of drug-related adverse events than what would normally be observed in the general population. Third, we did not perform challenge tests in the four patients who developed liver injury in this study. As we did not re-administer KFCSR, believing it to be the cause of the liver injury, we cannot be sure that the injury that occurred after KFCSR administration was indeed herb-induced liver injury. We could not eliminate the possibility of infections other than the hepatitis virus and the effects of food and alcohol consumption. Establishing a new diagnostic method is one of the major challenges of Kampo medicine [18, 19]. However, it is imperative to make well-defined diagnoses to clarify the true incidence and pathogenesis of herb-induced liver injury caused by Kampo medicine. We believe that physicians should also consider performing challenge tests with adequate preparation in keeping with all ethical aspects. Fourth, we used DDWJ2004CD to diagnose drug-induced liver injury [13]. According to the International expert panel, cases should be considered drug-induced liver injury based on the following criteria: ALT or AST $>5\times$ upper normal limit (UNL), ALP $>2\times$ UNL, ALT or AST $3\times$ UNL, and total bilirubin $\geq 2\times$ UNL [20]. Therefore, considering these criteria, only Cases 2was diagnosed with herb-induced liver injury, thereby reducing the incidence of herb-induced liver injury due to KFCSR to 2.7%. Therefore, DDWJ2004CD may lack validity to diagnose KFCSR. Fifth, we conducted this study in a limited geographical area. It is well-established that inflammation and immune responses differ by race and ethnicity. African Americans are at a higher risk of developing chronic herb-induced liver injury (defined as persistent liver alteration beyond 6 months of herb-induced liver injury recognition), while Asians are associated with earlier development of liver-related death or liver transplantation [21]. We do not know the extent to which the genetic predisposition, such as that associated with ethnicity, influences the development of KFCSR-induced liver injury. We cannot deny that individuals living in close proximity in the same geographical area may be particularly susceptible to this type of injury, which affects the generalizability of our findings.

There is a large discrepancy between the approximately 1% incidence reported by both Itoh *et al.* [12] and Mantani *et al.* [17] and our calculated rate of 10.8%. Therefore, we strongly believe that the incidence of KFCSR-induced liver injury and its mechanism of occurrence should be investigated in a larger sample population in a more general practice setting throughout Japan.

We did not use the DLST in our study, as we discovered that although DLST is included in the DDWJ2004CD, it gives rise to several false positives when Kampo formulae or crude drugs are tested, even though they are not the true cause of the disease [22, 23]. This indicates that using DLST as the basis for diagnosis in cases where adverse events were suspected to be caused by Kampo formulae or crude drugs may confuse and mislead the diagnosis. Thus, we did not implement DLST in this study.

KFCSRs are an important group of formulations that are essential for dispensing safe and effective treatment with Kampo medicine to patients. Our aim was to clarify the incidence and mechanism of adverse effects caused by KFCSR, so that it can be used more safely and widely in clinical practice. Based on our findings, future studies are warranted to verify our results and make KFCSRs more effective for use in patients. Moreover, as most cases of KFCSR-induced liver injury occur within 1–2 months of KFCSR administration in actual clinical practice, we strongly recommend that patients should be examined for liver injury using blood tests within 2 months of the initiation of administration of KFCSRs, especially when they are administered for the first time.

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ETHICAL STATEMENT

The study design was approved by the Ethics Committee of Joetsu General Hospital (Reference no. 220). Due to the retrospective nature of this study, the need to obtain informed patient consent was waived.

DATA STATEMENT

The data that support the findings of this study are available from the corresponding author, T.N., on reasonable request.

DECLARATIONS OF INTEREST

T. Nogami and M. Arai received lecture fees from Tsumura & Co., and their affiliation gained a research grant from Tsumura & Co.; however, this is unrelated to this study.

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