Drug-Induced Liver Injury by Dietary Supplements in Japan

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Recently, cases of drug-induced liver injury (DILI) by dietary supplements including so-called health foods and herbal medicines have increased in Japan. Much attention has been paid to DILI by dietary supplements since the reports of many cases of severe liver injury by Chinese dietary supplements in July 2002. The increased use of dietary supplements due to a health boom derived from the increase in patients with lifestyle-related illness and doctors’ knowledge of DILI by dietary supplements seems to have increased the reports of such cases. In this review, the present status of DILI by dietary supplements in Japan is discussed.

The first nationwide survey of DILI by dietary supplements was reported at the 33rd West Regional Meeting of the Japan Society of Hepatology in 1999. A questionnaire on DILI was sent to active members of the society, and twelve cases of DILI by dietary supplements were included in 2,561 DILI cases between 1989 and 1998. In this survey, DILI by dietary supplements accounted for only 0.5% of total DILI cases. The mean age was 52 years, and 50% were women.

After the reports of DILI cases by Chinese dietary supplements, the Japan Society of Hepatology surveyed DILI cases by dietary supplements. Thirty-one cases of DILI by dietary supplements during 2002 were identified. The mean age was 44 years (24–73 years), and 29 cases (94%) were women. In this survey, most cases (21 cases) were DILI by Chinese dietary supplements. The mean duration until the onset in all cases was 78 days (10–450 days), and in cases by Chinese dietary supplements was 83 days (11–450 days). Types of liver injury were 23 cases with acute hepatitis, 4 cases with severe hepatitis, 1 case with acute fulminant hepatitis, 1 case with sub-acute fulminant hepatitis, and 2 cases of late-onset hepatic failure. One case of death and 3 cases who received living donor liver transplantation were all due to Chinese dietary supplements.

At a workshop for DILI held in Digestive Disease Week-Japan 2004, Professor M. Onji and I had a chance to survey DILI cases by dietary supplements. In this study, DILI cases by Chinese dietary supplements were excluded. A questionnaire was sent to 14 speakers of the workshop, and 89 cases of DILI caused by dietary supplements were obtained. Figure 1 shows the distribution of age of the patients (mean age was 56 years) and 74% were women. Seventy-one cases (80%) had basal diseases, which consisted of liver diseases (27 cases), endocrine and metabolic diseases (10 cases), malignant tumors (9 cases) and cardiovascular diseases (7 cases). Seventy-one causal supplements were reported; 29 cases by Ukon (Curcuma), 9 cases by Agaricus, 2 cases by Life-pack, Kin-kei-gan, Propolis, So-Chu-Cha, Protein, Fukodain, Ao-jiru, Rei-shi Mushroom (Ganoderma Lucidum), Royal jelly and Russian Chaga, respectively. The most popular aim of the use of dietary supplements was for health (54 cases), followed by that for basal diseases (23 cases). Twenty-three cases were using more than
1 supplement simultaneously, and 53 cases were taking supplements together with approved drugs. Symptoms were observed in 58 cases; 40 cases with general fatigue, 17 cases with jaundice, 9 cases with appetite loss, 9 cases with nausea and vomiting, 8 cases with itching, 7 cases with fever, and 3 cases with eruption or urticaria.\(^3\)

As for the type of liver injury, hepatocellular injury type was the most popular (67 cases), followed by cholestatic type (13 cases) and mixed type (9 cases).\(^3\) The percentage of hepatocellular injury type was higher than that by approved drugs. Seventy cases presented with acute hepatitis, fulminant hepatitis occurred in 3 cases, and one case each of severe hepatitis and late onset of hepatic failure was observed. Figure 2 shows the duration until the onset of liver injury (162 days on average), which was much longer than that by approved drugs.\(^3\) Most patients (56 cases) recovered without special therapies after stopping the use of supplements. Three cases with fulminant hepatitis were subjected to plasma exchange, and one case received living donor liver transplantation. Two cases died due to liver injury; one by fulminant hepatitis considered to be due to Russian Chaga, and the other by multiple organ failure after acute hepatitis due to Ukon.\(^3\)

DILI is classified into toxic and idiosyncratic types. Most DILI cases are the idiosyncratic type, which is further classified into allergic type and metabolic idiosyncratic type. It is yet unknown which type of DILI is common in DILI caused by dietary supplements, but the metabolic idiosyncratic type seems to be popular, since most cases are acute hepatitis type and the durations until the onset of liver injury are relatively long. However, until the characteristics of DILI by dietary supplements are clarified, this question remains unresolved.

DILI by dietary supplements is also a social problem in foreign countries.\(^5\) Recently, 3 sister cases of DILI by usnic acid, which often causes DILI in the United States, were reported from Taiwan.\(^5\) They acquired usnic acid from their relatives living in California.\(^5\) As observed in this example, it is very difficult to estimate how many people are taking such dietary supplements, because we can easily import them privately through the Internet.

The incidence of DILI by dietary supplements is considered to be lower than that by approved drugs, and there are two subjects which have to be resolved in the future. One is surveys for the actual situation of DILI by dietary supplements in Japan. In the United States, 40 million people are consuming at least one kind of supplement per week.\(^6\) However, the frequency of DILI by dietary supplements is not clear even in the United States. According to a recent report from Oregon University, 10 out of 20 patients who received liver transplantation due to fulminant liver failure had recently used dietary supplements.\(^7\) We have to know both the denominator of the people using dietary supplements and the numerator of patients with DILI by dietary supplements in order to calculate the incidence. Therefore, surveys of the numbers of people taking dietary supplements are important. Such information in Japan is very limited. Through a questionnaire to patients with digestive diseases who came to Kurume University Hospital and...
related hospitals, 326 patients were using dietary supplements.\(^8\) Popular supplements were vitamins (42%), Ukon (35%), Agaricus (16%) and garlic (13%).\(^8\) Similarly, by a questionnaire to 349 patients with urologic cancer who came to Kurahashi Central Hospital, 164 patients (47%) had used dietary supplements.\(^9\) Popular supplements were Agaricus (52 cases), vitamins (35 cases), Propolis (21 cases) and Ukon (16 cases).\(^9\)

Another important subject is to enlighten people to the fact that even dietary supplements may cause liver injury just as approved drugs do, and to consult doctors for the treatment and prevention of diseases without easy dependence on dietary supplements.

References