Recent Status of Drug-induced Liver Injury and Its Problems in Japan

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Abstract

Adverse drug reactions are becoming a social issue in recent years. Liver injury, which could become fulminant and even fatal, is particularly a focus of growing concern. Based on the etiology, drug-induced liver injury (DILI) is classified to predictable and unpredictable (idiosyncratic) liver injury, and the latter cases are further classified into allergic and non-allergic liver injury. When diagnosing DILI into specific types, the diagnostic criteria proposed at the workshop during Digestive Disease Week-Japan 2004, which uses the ALT and ALP levels at the time of diagnosis and the total score from the eight diagnostic items, are widely used in Japan.

According to the survey of 1,676 cases presented at the 44th Annual Meeting of the Japan Society of Hepatology, the duration from the start of medication to the onset of liver injury was 30 days or less in 62% of cases, with as many as 16% took longer than 90 days. While the most frequently observed causal drugs were antibiotics and antipyretic/analgesic/anti-inflammatory drugs, recent increases in dietary supplements and Chinese herbal medicines were notable. The possible involvement of these agents demands special attention in diagnosis, considering liver injury take longer to manifest.

Key words Diagnostic criteria, Drug-induced lymphocyte stimulation test (DLST), Causal drug, Dietary supplement

Introduction

Recently, adverse drug reactions are becoming an issue in the society as well. In particular, liver injury, which could become fulminant and even fatal, is a focus of growing concern. Because most drugs are metabolized in the liver, it inevitably suffers the risk of adverse reactions. Drug-induced liver injury (DILI) in recent years is caused by not only the prescription drugs but also by folk remedies and dietary supplements. DILI is defined as hepatocellular injury and intrahepatic cholestasis resulting from drug administration. While the term may refer to broader range of drug-induced liver diseases (liver tumors, fatty liver, etc.) in Europe and North America, the above-mentioned narrower definition is more widely used in Japan.

Classification of DILI

Based on the etiology, DILI is roughly divided into predictable type and unpredictable (idiosyncratic) type. Predictable cases, such as acetaminophen-induced liver injury which is concentration-dependent and relatively frequent in Europe and North America, are rather exceptional cases; most cases of DILI are unpredictable, which are caused by idiosyncrasies of a patient. Idiosyncratic DILI is further divided into allergic DILI that involve a patient's allergic mechanism or non-allergic (metabolic idiosyncratic) DILI that is caused by the production of highly hepatotoxic metabolites due to individual idiosyncrasy. The diagnosis of allergic DILI can be made more confidently when there are signs of allergy such as fever, skin rash, itching, and eosinophilia. On the other hand, metabolic idiosyncratic DILI is

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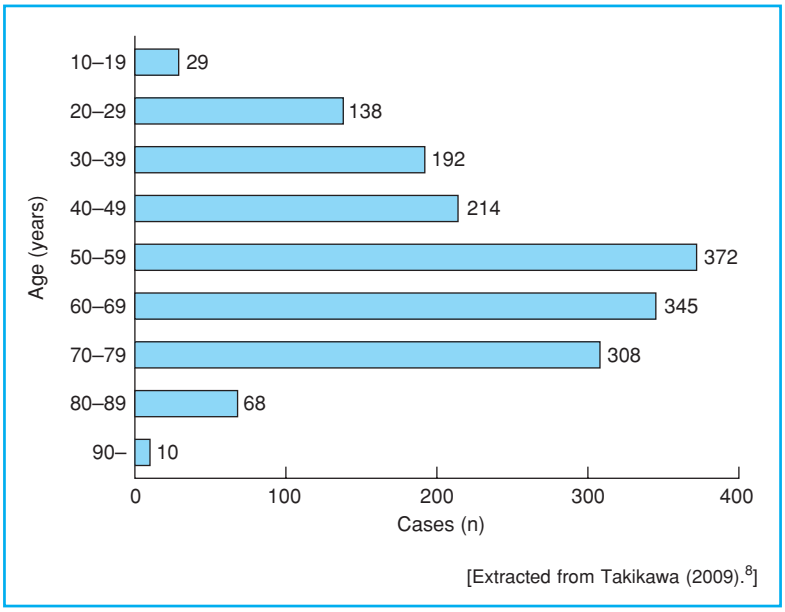

Fig. 1 Age distribution of 1,676 cases of drug-induced liver injury from January 1997 to December 2006

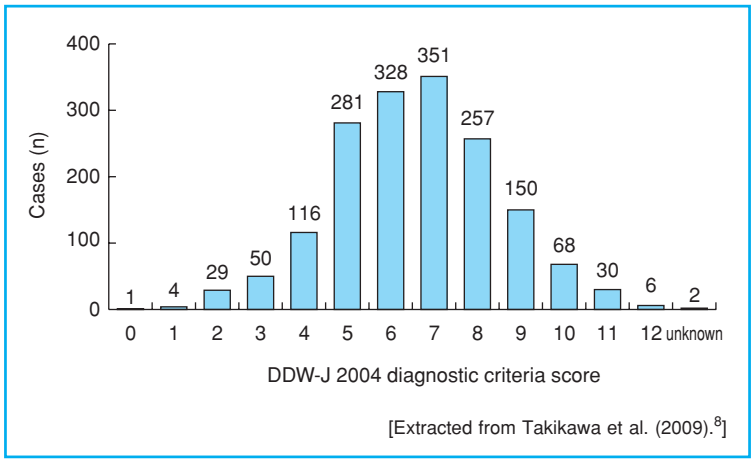

Fig. 2 Distribution of DDW-J 2004 diagnostic criteria scores in 1,676 cases of drug-induced liver injury from January 1997 to December 2006

difficult to diagnose, and the identification of the specific metabolite in a particular individual is extremely difficult.

In terms of the clinical signature of liver injury, DILI is classified into the three types; hepatocellular, cholestatic, and mixed. The ALT and ALP levels at the time of diagnosis are used expediently to make an assessment.

Diagnosis of DILI

The two key elements in the diagnosis of DILI are the time relationship between the drug administration and appearance/disappearance of liver injury and the exclusion of other potential causes. Careful history taking is essential because folk remedies or dietary supplements casually used by a patient can be the causal drug.

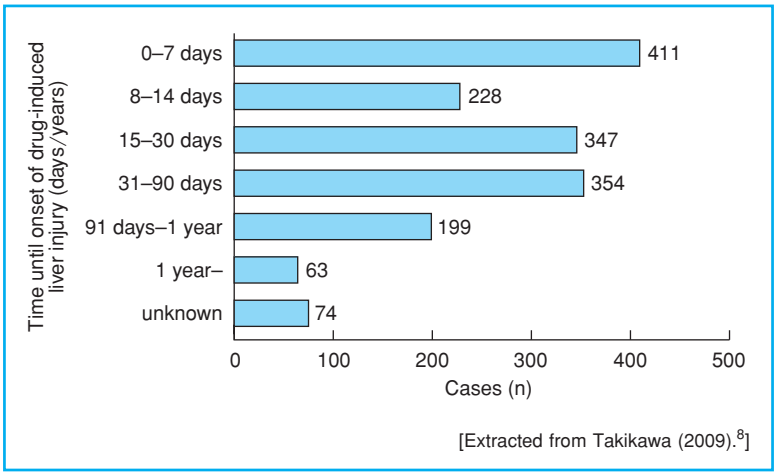

Fig. 3 Duration until onset in 1,676 cases of drug-induced liver injury from January 1997 to December 2006

Table 1 Comparison of drug-induced liver injury cases between the Years 1997–2006 and 1989–1998 (based on the analysis of 879 cases in which the causal drug was identified to a single source)

Causal drug	1997–2006	1989–1998
Antibiotics	14.3% (126 cases)	22.0%
Psychiatric & neurological drugs	10.1% (89 cases)	7.8%
Dietary supplements	10.0% (88 cases)	0.7%
Antipyretic/analgesic/antiinflammatory drugs	9.9% (87 cases)	11.9%
Cardiovascular drugs	7.5% (66 cases)	6.5%
Chinese herbal medicines	7.1% (62 cases)	4.7%
Gastrointestinal drugs	6.1% (54 cases)	7.4%
Over-the-counter drugs	5.5% (48 cases)	5.8%
Hormones	3.6% (32 cases)	4.6%
Antiallergic drugs	3.2% (28 cases)	3.7%
Hematopoietic & hemagglutination drugs	2.8% (25 cases)	3.6%
Antilipidemic drugs	2.7% (24 cases)	0.7%
Anticancer drugs	2.6% (23 cases)	2.9%

[Quoted from Horiike et al. (2008).[7] (in Japanese)]

In Japan, the diagnostic criteria for DILI proposed in 1978[1] had been used for a long time. Then, the diagnostic criteria proposed at the International Consensus Meeting, which was published in 1993,[2] were found useful in the case assessment among Japanese patients.[3] Although they are still being used in other countries, the 1993 criteria posed various problems to be applied widely in Japan—namely, the need to adapt the drug-induced lymphocyte stimulation test (DLST). Consequently, discussions were held at the symposium during the Digestive Disease Week-Japan (DDW-J) in 2002[4] and the workshop in the DDW-J 2004, and the new diagnostic criteria for DILI were proposed,[5,6] which are widely used in Japan now.

Recent Trend of DILI in Japan

At the 44th Annual Meeting of the Japan Society of Hepatology (Chairman: Dr. Morikazu Onji) in June 2008, an analysis of 1,676 cases of DILI accumulated from 29 facilities over ten years from January 1997 to December 2006 was presented.[7,8] The patients included 721 males and 955 females (average age, 55 years); the age distribution is shown in **Fig. 1**. The types of liver injury were: 59% hepatocellular injury, 20% mixed, and 20% cholestatic. Compared to the analysis of 2,515 DILI cases during the ten years from 1989 to 1998,[9] the percentage of hepatocellular injury had increased from the 46% to 59%. DLST was performed in 61% of the cases, of which 33% were positive.

Figure 2 shows the distribution of scores based on the DILI diagnostic criteria from the DDW-J 2004 workshop.[5,6] The data indicate a good sensitivity, as 87.9% of the cases are diagnosed as "highly probable" (5 points or more) and 97.8% were diagnosed as "possible" and above (3 points or more).

Figure 3 shows the duration from the start of medication to the onset of liver injury among patients. When the cases of unknown duration are excluded, the cumulative percentages show that 26% of the DILI cases occurred within 7 days, 40% in 14 days or less, 62% in 30 days or less, 84% in 90 days or less, and as many as 16% occurred after 90 days.[8]

Table 1 shows the proportions of causal drugs from the 1997–2006 study[7] in comparison with the 1989–1998 study by Tameda et al. (1999).[9] Antibiotics and antipyretic/analgesic/antiinflammatory drugs still remain high (14.3% and 9.9%, respectively) compared to ten years ago.[9] On the other hand, dietary supplements and Chinese herbal medicines both show increases (10.0% and 7.1%, respectively). The increase in the share of dietary supplements is particularly pronounced. The proportion of antilipidemic drugs, although still low at 2.7%, also increased, presumably reflecting the recent increase in the variety of prescription. It should be noted that dietary supplements and Chinese herbal medicines take longer to manifest than other drugs (dietary supplements, 260 days; Chinese herbal medicines, 124 days; mean of other drugs, 62 days), which calls for special attention in the diagnosis of DILI.

Treatment of DILI

The basic strategy when treating DILI is to discontinue medication, which usually cures the patient without any further treatment. A problem at present, however, is the lack of appropriate standards for discontinuation. Here I introduce a few guidelines from my own cases as reference.[10]

1. When ALT level is 100 IU/L or higher but less then 300 IU/L, carefully observe the progress at intervals of several days.
2. If ALT level is increased to 300 IU/L or higher, discontinue medication.
3. If total bilirubin is increased to 3 mg/dL or higher, or if the patient shows the symptoms consistent with liver injury or skin rashes, discontinue medication.

In the case of hepatocellular injury, intravenous glycyrrhizin injection or oral administration of ursodeoxycholic acid is commonly used. However, no evidence of their effectiveness has been obtained at present.

In the case of cholestatic DILI, treatment may include the administration of ursodeoxycholic acid, prednisolone, and/or phenobarbital. A fulminant case requires hemodialysis and continuous hemodiafiltration; when these treatments are ineffective, liver transplantation will be the only option to save the life of a patient.

Problems of the DDW-J 2004 Diagnostic Criteria and Future Prospects

While the diagnostic criteria of the DDW-J 2004 workshop are widely used in Japan at present, there are still issues that should be examined.[11] Further study through accumulation of cases and future reevaluation will be necessary.

In other countries, prospective accumulation of DILI cases has been underway. In Japan, too, the strong need of a project has been voiced to collect specimens from multiple institutions for the purpose of the prospective accumulation of cases and the search for biomarkers associated with the development of DILI. In cooperation with the National Institute of Health Sciences of Japan, a collaborative project is currently being planned with the participation of more than 30 facilities, which is to be launched soon. Our future goal is to be able to identify patients with a high risk of DILI by performing simple and easy screening of various biomarkers in advance.

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