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REVIEW

Practical guidelines for diagnosis and early management of drug-induced liver injury

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Abstract

The spectrum of drug-induced liver injury (DILI) is both diverse and complex. The first step in diagnosis is a suspicion of DILI based on careful consideration of recent comprehensive reports on the disease. There are some situations in which the suspicion of DILI is particularly strong. Exclusion of other possible etiologies according to the pattern of liver injury is essential for the diagnosis. In patients with suspected DILI, diagnostic scales, such as the Councils for International Organizations of Medical Sciences/ Roussel Uclaf Causality Assessment Method (CIOMS/ RUCAM) scale, may be helpful for the final diagnosis. Early management of DILI involves prompt withdrawal of the drug suspected of being responsible, according to serum levels of alanine aminotransferase (ALT), alkaline phosphatase (ALP), and total bilirubin (T-Bil). However, as DILI patients may show resolution of liver injury without discontinuation of the drug, it should be carefully evaluated whether the suspected drug should be discontinued immediately with adequate consideration of the importance of the medication.

Key words: Diagnosis; Drug-induced liver injury; Guidelines; Management

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INTRODUCTION

Drug-induced liver injury (DILI) is a common liver disease which generally occurs between 5 and 90 d after drug ingestion. The clinical picture of the disease is variable, ranging from transient mild elevation of liver enzymes to fulminant liver failure leading to death. DILI has been reported to be a cause of fulminant liver failure in 13%-30% of cases[1-3]. DILI is divided into three types: hepatocellular, cholestatic, and mixed according to the Councils for International Organizations of Medical Sciences (CIOMS)[4,5]. Hepatocellular type is defined by alanine aminotransferase (ALT) > 2 ULN (upper limits of normal) or R $\geqslant$ 5, where R is the ratio of serum activity of ALT/serum activity of alkaline phosphatase (ALP), both of which are expressed as multiples of the ULN. Liver injury is likely to be more severe in hepatocellular type than in cholestatic/mixed type, and patients with elevated bilirubin levels in hepatocellular liver injury indicating serious liver injury with fatalities, are found at a rate of 0.7 to 1.3/100 000 individuals receiving a given drug[2]. Cholestatic type is defined by ALP > 2 ULN or R $\leqslant$ 2 and mixed type is defined by ALT > 2 ULN and 2 < R < 5. Patients with cholestatic/ mixed type are likely to develop chronic disease more frequently than those with hepatocellular type[6]. For most drugs, the risk of liver injury is estimated to be 1-10/100 000 persons exposed. A recent report indicated that DILI occurs in 1/100 patients hospitalized in internal medicine departments[7]. Thus, DILI is not a rare condition and sometimes leads to serious disease. Rapid and accurate diagnosis of DILI is important in daily practice. However, diagnosis of DILI is not easy and is mainly based on circumstantial evidence. As there is no gold standard for diagnosis, it is essential to exclude other possible etiologies for accurate diagnosis. A number of scoring systems have been proposed,

but even experts may make different judgments using these systems[8]. This review summarizes recent trends regarding DILI and proposes practical guidelines for its diagnosis and early management.

RECENT REPORTS ON DILI

A recent report on DILI based on the database of the World Health Organization (WHO) indicated that the number of cases of DILI has been increasing since the 1990s[9]. The WHO began monitoring adverse drug reactions in 1968, and there are more than 3 million reports on their database (http://www.who-umc.org). This large database is useful for obtaining information on previous reports regarding adverse reactions to drugs. Acetaminophen, drugs against human immunodeficiency virus (HIV), troglitazone, anti-convulsants (such as valproate), analgesics, antibiotics, and anti-cancer drugs are common causative agents of DILI with fatalities (Table 1)[9]. Therefore, particular attention should be paid to patients taking one or more of these drugs who show liver injury. Analysis of 461 cases in Spain over a 10-year period indicated that amoxicillin/clavulanate was the most common drug involved in DILI (59/461 cases, 12.8%)[10]. Moreover, in addition to amoxicillin/clavulanate, they reported that bentazepam, atorvastatin, and captopril were frequent causative drugs leading to chronic liver damage[6]. In a retrospective study in Italy, hydroxymethylglutaryl-CoA reductase inhibitors were the most frequent causative drugs among 1069 cases of DILI (4.5% of cases of adverse drug reactions)[11]. Other studies also showed acetaminophen, anti-retroviral therapy, antibiotics, lipid-lowering drugs, and anti-convulsants to be responsible for DILI[12-18]. In recent analyses in Asia, traditional alternative medicines were reported to be the most common causes of DILI, in contrast to those in Western countries[19]. Table 2 summarizes the drugs suspected to be responsible for DILI and the types of liver injury reported in the literature from various regions[3,6,7,10,12,17-19]. In general, antibiotics, non-steroidal anti-inflammatory drugs, and anti-convulsants are frequent causative drugs of DILI. Importantly, although not shown in Table 2, two or more drugs were suspected to be responsible for DILI in about 10% of cases[10,13]. Furthermore, it is notable that the incidences of DILI caused by herbal remedies or traditional medicines have been increasing over the last decade. The causative drugs for DILI are therefore becoming more diverse and complex. The first and most important step in managing cases of suspected DILI is to gain a detailed understanding of the causative drugs. In the United States of America, the Food and Drug Administration (FDA) records drug toxicity (http://www.fda.gov/medwatch), and the Drug Induced Liver Injury Network was established in 2003 to collect data on DILI in a prospective manner[1]. A similar network is also in place in Spain[6]. A worldwide network which collects all the reports on adverse drug reactions is needed to provide comprehensive information on DILI, which would facilitate accurate diagnosis and early management.

Table 1 Common causative agents of drug-induced liver injury with fatalities fatalities

Drug	*n* (%)
Acetaminophen	305 (16.9)
Anti-HIV[1]	
Stavudine, didanosine, nevirapine, zidovudine	303 (16.8)
Troglitazone	211 (11.7)
Anticonvulsants (valproate, phenytoin)	187 (10.3)
Anti-cancer	223 (12.3)
Flutamide	59 (3.3)
Cyclophosphamide	56 (3.1)
Methotrexate	55 (3.0)
Cytarabine	53 (2.9)
Antibiotics	158 (8.7)
Trovafloxacin	57 (3.2)
Sulfa/trimethoprim	52 (2.9)
Clarithromycin	51 (2.8)
Anesthetic	
Halothane	85 (4.8)
Anti-tuberculosis	
Isoniazid	57 (3.2)
Diclofenac	56 (3.1)
Oxycodone	56 (3.1)

[1]human immunodeficiency virus.

PRACTICAL DIAGNOSIS OF DILI

Situations in which DILI should be suspected

In daily clinical practice, DILI can always be a cause of liver injury in patients taking medications. However, there are some situations in which DILI should be particularly suspected and are as follows[20]: (1) Start of a new drug in the past 3 mo, (2) Presence of rash or eosinophilia, (3) Mixed type (hepatocellular and cholestatic) liver injury, (4) Cholestasis with normal hepatobiliary imaging and (5) Acute or chronic hepatitis without autoantibodies or hypergammaglobulinemia. Although DILI cannot be excluded if patients with any type of liver injury do not meet these criteria, their consideration may lead to early diagnosis of DILI.

Risk factors for DILI

Recognition of risk factors provides clues for the diagnosis of DILI, and some scoring systems include these elements. Host factors which may be associated with DILI are listed in Table 3. Age, gender, pregnancy, and alcohol intake are estimated as risk factors for patients, and liver injury with these risk factors is thought to be related to acute cytolytic hepatitis[21]. In a recent analysis, age was reported to be the most important determinant in biochemical expression of amoxicillin/clavulanate hepatotoxicity, probably because of the slower drug elimination related to advanced age[22]. In contrast, adverse events associated with valproate or erythromycin are more common in childhood[23]. On the other hand, a retrospective study indicated that most patients with drug-induced acute liver failure undergoing

Table 2 Drugs suspected of being responsible for at least two cases of drug-induced liver injury and the types of liver injury reported in recent literature

Use	Drugs	Hepatocellular	Cholestatic	Mixed
Anti-microbial	Amoxicillin-clavulanate	28	26	23
	Azithromycin	0	8	0
	Trovafloxacin	5	0	1
	Erythromycin	2	4	3
	Clindamycin	2	0	0
	Nitrofurantoin	1	1	0
	Levofloxacin	0	0	1
	Ciprofloxacin	2	1	1
	Flucloxacillin	0	7	1
	Sulfasalazine	1	0	1
	INH + RIP + PIZ	24	6	32
	HAART	4	1	1
	Dapsone	2	0	0
Anti-inflammatory	Acetaminophen	40	0	0
	Diclofenac	18	8	3
	Nimesulide	7	2	0
	Ibuprofen	8	3	9
Anti-convulsant	Carbamazepine	6	1	3
	Valproic acid	4	1	3
	Bentazepam	5	0	2
Psychiatric	Paroxetine	4	1	2
	Disulfiram	2	0	0
	Tetrabamate	6	1	0
Anti-cancer	Flutamide	12	1	5
	Methotrexate	3	0	0
Lipid-lowering	Atorvastatin	6	2	2
	Fenofibrate	1	0	2
Gastrointestinal	Ebrotidine	23	0	2
For circulation	Captopril	1	0	1
Anti-coagulant	Ticlopidine	8	5	1
For endocrine	Thiamazole	1	4	0
Immunosuppressant	Azathioprine	5	4	2
Others	Medical herbs	26	3	2
	OTC health supplements	3	0	0

INH: Isoniazid; RIP: Rifampicin; PIZ: Pirazinamide. HAART: Highly active antiretroviral therapy. 40 cases from United States of America between 1998 and 2006; 28 cases from Spain between 1995-2005; 88 cases from Switzerland between 1996 and 2000; 461 cases from Spain between 1994 and 2004; 29 cases from United States of America between 1999 and 2003; 34 cases from France between 1997 and 2000; 77 cases from Sweden between 1995 and 2005; 31 cases from Asia between 2004 and 2006.

liver transplantation were female[24]. Thus, age and female gender may affect the clinical course of DILI. As immune responses to drugs and altered drug metabolism are possible mechanisms in DILI pathogenesis, different immune status or drug metabolism according to age or gender may lead to differences in the occurrence of DILI[25,26]. However, Shapiro and Lewis reported that factors such as age (over 55 years old), gender (female dominant), or the history of alcohol intake were not specific for DILI based on the evaluation of recent DILI cases using the CIOMS/RUCAM scale[27]. Therefore, risk factors for DILI must be analyzed carefully in future. Moreover, genetic factors for drug metabolism, such as polymorphisms of cytochrome P (CYP) 450 or deficiency of N-acetyltransferase, have been reported to contribute to DILI[28,29]. Interestingly, a recent report suggested an association between the daily dose of drug ingested and idiosyncratic DILI, and the number of cases and poor outcome of DILI were reported to increase in a dose-dependent manner[30]. Furthermore, underlying liver disease or systemic viral infection may increase susceptibility to DILI. In particular, DILI caused by anti-tuberculous therapy is known to be increased in patients with hepatitis B or C virus infection[31]. Anti-retroviral therapy in HIV infection was reported to induce severe hepatitis and lead to acute liver failure[32]. The mechanisms by which HIV infection predisposes patients to severe DILI are unknown, but activation or sensitization of the innate immune system by HIV infection may be involved. Moreover, hepatic steatosis in nonalcoholic fatty liver disease (NAFLD) increases the risk of DILI[33]. Mitochondrial dysfunction or the existence of oxidative stress seen in NAFLD may affect the occurrence and severity of DILI.

Clinical diagnosis of DILI

There are few clinical features associated specifically with DILI. Although fever, rash, arthralgia, and eosinophilia are symptoms and signs of an immunoallergic reaction to a drug, they can also be seen without taking any drugs and the frequencies in patients with DILI are not high. General fatigue, appetite loss, and splenomegaly, often seen in patients with viral hepatitis that may be helpful for differential diagnosis at initial presentation, are also

Table 3 Axes and scores of four representative scales utilized for diagnosis of drug-induced liver injury

NADRPS		CIOMS/RUCAM		M&V		DDW-J	
Axis	**Score**	**Axis**	**Score**	**Axis**	**Score**	**Axis**	**Score**
Chronological criteria		Chronological criteria		Chronological criteria		Chronological criteria	
Illegibility in onset	-1 to +2	From drug intake until onset	+1 to +2	From drug intake until onset	+1 to +3	From drug intake until onset	+1 to +2
		From drug withdrawal until onset	0 to +1	From drug withdrawal until onset	-3 to +3	From drug withdrawal until onset	0 to +1
Course of the reaction							
	0 to +1	Course of the reaction	-2 to +3	Course of the reaction	-3 to +3	Course of the reaction	-2 to +3
		Risk factors Age	0 to +1			Risk factors	
		Alcohol (or Pregnancy)[1]	0 to +1			Alcohol (or Pregnancy)[1]	0 to +1
		Concomitant therapy	-3 to 0				
Exclusion of other causes	-1 to +2	Exclusion of other causes	-3 to +2	Exclusion of other causes	-3 to +3	Exclusion of other causes	-3 to +2
		Previous information	0 to +2	Previous information	0 to +2	Previous information	0 to +1
Rechallenge	-1 to +2	Rechallenge	-2 to +3	Rechallenge	0 to +3	Rechallenge	0 to +3
Placebo response	0 to +1						
Drug concentration and monitoring	0 to +1			Extrahepatic manifestations rash, fever, arthralgia, eosinophilia, cytopenia	0 to +3	Extrahepatic manifestations eosinophilia	0 to +1
Dose relationship	0 to +1						
Previous exposure and cross-reactivity	0 to +1						
Any objective evidence	0 to +1					DLST	0 to +2
⩾ 9	Definitive	> 8	Definitive	⩾ 18	Definitive	⩾ 5	Definitive
5 to 8	Probable	6 to 8	Probable	14 to 17	Probable	3 to 4	Probable
1 to 4	Possible	3 to 5	Possible	10 to 13	Possible	⩽ 2	Unlikely
⩽ 0	Unlikely	1 to 2	Unlikely	6 to 9	Unlikely		
		⩽ 0	Excluded	⩽ 5	Excluded		

[1]Cholestatic/Mixed cases; DLST: Drug lymphocyte stimulation test.

not common in non-fulminant DILI. As there are many causes of liver injury, it is essential to exclude other etiologies in the diagnosis of DILI. Other etiologies include viral hepatitis (hepatitis A virus, hepatitis B virus, hepatitis C virus, hepatitis E virus, EB virus, cytomegalovirus, human herpes virus-6, parvovirus B19, *etc*.), biliary diseases such as cholelithiasis, alcohol abuse, NAFLD, autoimmune liver diseases, and hereditary diseases, such as hemochromatosis, α_1-antitrypsin deficiency, and Wilson's disease. Among these possible causes of liver injury, diagnosis of acute onset autoimmune hepatitis (AIH) is sometimes difficult, because scores using the International Autoimmune Hepatitis Group scoring system for the diagnosis of AIH, serum IgG levels or antinuclear antibody titers are often low in acute AIH. Histological examination of the liver may be useful for the differential diagnosis. Taken together, a low threshold of suspicion, thorough history including recent and past drug exposure, exclusion of other possible etiologies, or occupational hazards with exposure to potential toxins, are important in making an accurate diagnosis of DILI[20,34]. Some clinical scales are available for the diagnosis of DILI. However, it is impractical to apply these diagnostic scales for each patient with liver injury taking medications. In addition, most patients take more than one drug, and identification of a single drug as a causative agent is difficult, even in cases where DILI is strongly suspected, using these scales. Moreover, patients with underlying liver or systemic diseases which also affect liver biochemical tests, complicate the diagnosis of DILI.

Clinical scales available for diagnosis of DILI (Table 3)

As there are no standard criteria for diagnosis of DILI, various clinical scales have been developed. The Naranjo Adverse Drug Reactions Probability Scale (NADRPS) was proposed in 1981 for assessment of adverse drug reactions[35]. NADRPS has been widely used for DILI due to its simplicity and wide applicability, despite not being developed specifically for diagnosis of DILI. Although simplicity is important for practical use, NADRPS has been reported to have low sensitivity and negative predictive values, and to exhibit a limited capability to distinguish among adjacent categories of probability such as "possible" and "probable"[36]. In the early 1990s, the diagnostic scale called the Council for International Organizations of Medical Sciences (CIOMS) or Roussel Uclaf Causality Assessment Method (RUCAM), was proposed at the International Consensus Meeting by Danan and Benichou[4]. It was also called the French method, because Danan had previously reported the diagnostic criteria for acute cytolytic hepatitis in France[21]. CIOMS/RUCAM is applied for classification of the pattern of liver injury, hepatocellular type, cholestatic type, or mixed type, as described above. This scale is determined by a score based on 7 criteria, including temporal relationship, clinical course (response after withdrawal of drug), risk factors, concomitant drugs, exclusion of other non-drug

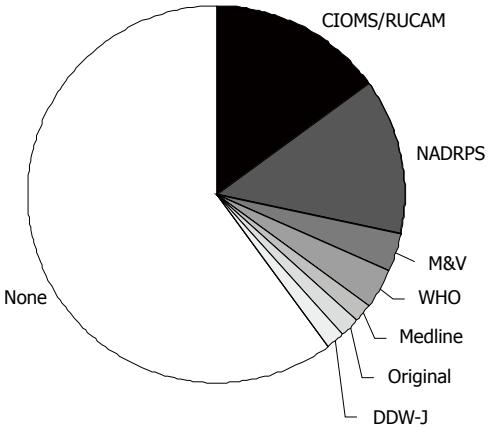

Figure 1 Percentages of methods for causality assessment utilized for diagnosis of DILI, reported during the last decade.

etiologies, likelihood of a reaction based on package labeling, and rechallenge. It has been widely used as a standardized scale with high reliability, reproducibility, and specificity. More recently, Maria and Victorino (M&V) reported a scale called the clinical diagnostic scale (CDS), which simplified the CIOMS/RUCAM using only 5 criteria[37]. It has often been noted that false negative judgments are often made in cholestatic DILI cases because the pattern of liver injury is not taken into consideration in the M&V scale[38]. Moreover, DILI cases with long latency periods and evolution to chronic disease after withdrawal (especially cholestatic type) were poorly diagnosed, and there was no agreement in cases of fulminant hepatitis[39]. The M&V scale emphasizes the immunoallergic reactions, such as extrahepatic manifestations[40]. In Japan, a diagnostic scale was proposed by reference to the CIOMS/RUCAM scale in Digestive Disease Week Japan (DDW-J) 2004, and includes a drug-lymphocyte stimulation test (DLST) as a diagnostic factor[41]. The DDW-J scale was reported to have higher sensitivity than the CIOMS/RUCAM (93.8% *vs* 77.8%, respectively) in the analysis of 127 Japanese patients. However, this scale must be evaluated in non-Japanese patients to verify its universal usefulness.

A review of 61 case reports of DILI in the PubMed database over the last decade regarding diagnostic methods used[42-102] (Figure 1, Table 4) revealed that the CIOMS/RUCAM was the most widely utilized for diagnosis of DILI (10/61 case reports, 16.4%), followed by NADRPS (8/61, 13.1%), M&V (CDS) (2/61, 3.3%), WHO database (2/61, 3.3%), Medline (1/61, 1.6%), Original (1/61, 1.6%), DDW-J (1/61, 1.6%), and none (38/61, 62.3%). The case reports using the WHO database[88,98] or Medline[77] based DILI diagnosis on reports of the suspected drug as a causative drug in the database in addition to circumstantial evidence (history of drug intake, onset of liver injury, and exclusion of other causes). In the case of original criteria[73], DILI diagnosis was made using the following criteria: occurrence of hepatic damage directly related to drug administration, exclusion of other causes of hepatitis, recovery of hepatic function tests after cessation of drug therapy, and liver histology. Although the CIOMS/RUCAM scale is the most widely used and thus currently seems to be the standard method for diagnosis of DILI, it should be emphasized that many physicians still make a diagnosis of DILI based on their own judgment probably because of the complexity of the scoring systems available.

Additional tests to confirm the diagnosis of DILI and identify a single causative drug

As mentioned above, patients are often taking several drugs only one of which is responsible for liver injury in most cases. However, even when clinical scales for DILI strongly suggest a given drug as a cause of liver injury, identification of the single causative drug cannot be established with these scales. Rechallenge with a potential causative drug to establish a diagnosis is one of the diagnostic methods in the CIOMS/RUCAM criteria[4,21]; however, it is not advised and may be contraindicated from an ethical viewpoint. As an alternative way to establish the diagnosis of DILI and the identification of a single causative drug, some additional tests using samples from the patient, such as peripheral blood, could be helpful. One of the most commonly used methods is DLST, which is performed as follows[103]: Lymphocytes collected from the heparinized peripheral blood of patients are incubated with various dilutions of the suspected causative drug. Lymphocyte proliferative response is evaluated by monitoring ^{3}H-thymidine uptake. DLST is widely used in Japan and is incorporated into the diagnostic criteria in Japan (DDW-J scale). However, sensitivity is around 50% and the lymphocyte response to the suspected causative drug may not necessarily be related to liver injury. Another test using peripheral blood of patients is the leukocyte migration test (LMT), which has been reported to be more useful than DLST[104]. This test involves assaying the chemotaxis of granulocytes from one chamber to another chamber containing mononuclear cells, due to the chemotactic factor produced by the mononuclear cells after incubation with the suspected drug solution. Furthermore, Murata *et al*[105] reported a cytokine production test as a method to analyze the immunological pathogenesis of DILI, which also showed high sensitivity for diagnosis. In this analysis, HepG2 cells, which reserve the activities of metabolic enzyme such as CYT450, are first incubated with the suspected drug diluents, and the mixtures of the extract and culture medium of HepG2 are then incubated with peripheral blood lymphocytes isolated from the patients. Intracytoplasmic cytokine profiles of the lymphocytes, such as interferon-γ, tumor necrosis factor-α, or interleukin-2, are finally evaluated by flow cytometry. Although these tests are useful methods for the diagnosis or identification of a single causative drug, they are not simple to perform, and may not be feasible for routine examination. However, if a single causative drug cannot be determined, patients may have to avoid several drugs, mostly non-hepatotoxic drugs, for the

Table 4 Diagnostic methods used for diagnosis of drug-induced liver injury during the last decade

Drug	Type[2]	Criteria	Country	Yr
Acetoaminophen[1]	H	None	Italy	2008
Dexketoprofen trometamol	H	None	Spain	2008
Anabolic-androgenic steroids	C	None	Mexico	2008
Quizalofop-p-ethyl	M	CIOMS/RUCAM	Greece	2007
Amoxicillin/clavulanate	M	None	USA	2007
Fenofibrate	H	None	Poland	2007
INH/RMP/PZA	M	None	USA	2007
Risperidone, Quetiapine	C	NADRPS	USA	2007
Clindamycin	C	NADRPS	Turkey	2007
Bupropion	M	CIOMS/RUCAM, M&V	USA	2007
Flutamide, Cyproterone	H	CIOMS/RUCAM	Spain	2007
Levothyroxine	H	DDW-J	Japan	2007
5-Fluorouracil[1]	H, M	NADRPS	New Zealand	2007
Sairei-to	H	LMT[3]	Japan	2007
Terbinafine	H	NADRPS, CIOMS/RUCAM	USA	2007
Ezetimide	H	None	USA	2007
Terbinafine	M	None	USA	2007
Infliximab[1]	H, C	None	Colombia	2007
Methylenedioxymethamphetamine	M	None	Canada	2006
Methylprednisolone	H	NADRPS	Turkey	2006
Shen-min	H	CIOMS/RUCAM	China	2006
Nimesulide	H	None	Italy	2006
Nevirapine	H	None	France	2006
Sirolimus	H	None	Poland	2005
Amiodarone	H	None	Japan	2005
Proguanil, Chloroquine	M	CIOMS/RUCAM	France	2005
Sulpyrine, Clarithromycin	H	None	Japan	2005
Glimepiride	C	None	Greece	2005
Flucloxacillin	M	None	Australia	2005
Sulbactam/ampicillin	C	NADRPS	Turkey	2004
Hydrochlorothiazide	M	NADRPS	Israel	2004
Ketoconazole	M	Original criteria	Korea	2003
Nimesulide	M	None	Turkey	2003
Ramipril	C	None	Canada	2003
Gemcitabine	M	None	USA	2003
Amoxicillin/clavulanate, Ciprofloxacin	H	Medline	USA	2003
Bupropion, Carbimazole	H	NADRPS	Singapole	2003
Ciprofloxacin	H	CIOMS/RUCAM	Germany	2003
6-Thioguanine	H	None	USA	2003
Terfenadine, Oxatomide	M	None	Japan	2002
Pioglitazone	M	None	USA	2002
Danazol	H	None	Japan	2001
Levofloxacin	H	None	USA	2001
Captopril[1]	M	None	Israel	2001
Pioglitazone	H	None	Japan	2001
Celecoxib	M	None	USA	2001
Nimesulide	M	WHO database	Switzerlamd	2001
Flutamide[1]	H	CIOMS/RUCAM, M&V	Spain	2001
Risperidone	C	None	Germany	2001
Zafirlukast	H	None	USA	2000
Troglitazone	H	None	USA	2000
Stavudine[1]	H	None	USA	2000
Bentazepam[1]	M	None	Spain	2000
Rosiglitazone	H	None	USA	2000
Nitrofurantoin	M	None	Israel	1999
Nimesulide[1]	H, M	CIOMS/RUCAM	Belgium	1998
Omeprazole	H	WHO database	Switzerlamd	1998
Troglitazone	M	None	USA	1998
Acarbose[1]	H	None	Japan	1998
Benzylpenicillin	H	CIOMS/RUCAM	Switzerland	1997
Terbinafine	M	None	France	1997

[1]Cases reported in multiple numbers, not in a single case, are summarized. [2]Type of liver injury. H: hepatocellular; C: cholestatic; M: mixed. [3]LMT, Lymphocyte migration test.

rest of their lives, seriously limiting treatment of other diseases. Therefore, these tests should be considered in selected cases.

Role of histological examination of the liver for the diagnosis of DILI

The features of liver histology in drug-induced hepatitis

are as follows: (1) demarcated perivenular (acinar zone 3) necrosis; (2) minimal hepatitis with canalicular cholestasis; (3) poorly developed portal inflammatory reaction; (4) abundant neutrophils; (5) abundant eosinophils; and (6) epithelioid-cell granulomas[106]. However, liver histology in DILI may not be diagnostic in most cases. Moreover, centrilobular necrosis with minimal portal inflammation is relatively characteristic of DILI, but similar histological features can be seen in acute-onset autoimmune hepatitis. Plasma cell infiltration in portal tracts, which is often prominent in autoimmune hepatitis, may be helpful for differential diagnosis in such cases. The major role of histological examination is therefore to exclude other possible causes of liver injury rather than to make a final diagnosis of DILI. Therefore, it is not recommended as a routine or early examination for the diagnosis of DILI.

EARLY MANAGEMENT FOR DILI

As described above, DILI has a wide spectrum of manifestations, ranging from asymptomatic mild biochemical abnormalities to severe hepatitis with jaundice. In most cases of DILI, liver injury would be expected to improve following discontinuation of the drug suspected to be responsible. On the other hand, some DILI patients may even show resolution of liver injury without discontinuation of the drug. Therefore, it should be carefully evaluated whether the suspected drug should be discontinued with adequate consideration of the importance of the medication. However, once liver injury progresses to acute liver failure, this has a high fatality rate without liver transplantation[107]. Although there are no definitive criteria for cessation of the suspected causative drug, some textbooks suggest that ALT less than 5 × ULN and no symptoms allow continuation of the suspected drug with close observation, whereas ALT of more than 8 × ULN indicates the need to discontinue the suspected drug[108,109]. Another textbook suggests that the suspected drug should be stopped only when abnormalities in serum bilirubin, albumin, or prothrombin time-international normalized ratio (PT-INR) are found in addition to elevated serum ALT[20]. Zimmerman reported that elevation of transaminase activities in combination with jaundice suggests serious liver injury with fatalities. These findings were discussed at the National Institutes of Health in Bethesda, and are recognized as Hy's rule for monitoring DILI, which states that elevation of liver enzymes (AST or ALT more than 3 × ULN or ALP more than 1.5 × ULN) in combination with elevated bilirubin (more than 3 × ULN) at any time after starting a new drug may imply serious liver injury and the suspected drug should be stopped[110]. Two recent studies have shown that hepatocellular liver injury with jaundice is sometimes fatal even if the suspected drug is stopped[9,10]. On the other hand, a recent study showed that cases fulfilling Hy's rule did not always lead to death from DILI[18]. As many drugs can induce asymptomatic elevation of liver enzyme levels without severe hepatotoxicity, mild elevations in transaminases do not always require withdrawal of the causative drug. Based on these observations, the FDA recently proposed draft guidelines (http://www.fda.gov/cder/guidance/7507dft.htm) in which ALT greater than 8 × ULN, ALT greater than 5 × ULN for two weeks, ALT greater than 3 × ULN in association with serum bilirubin greater than 2 × ULN, more than 1.5 × PT-INR, or symptoms of liver injury should be used to predict severe hepatotoxicity and recommend discontinuing the drug[2]. Hepatocellular liver injury with severe jaundice should be treated carefully, and requires prompt referral to a center with hepatologists. As mentioned above, severe liver injury and fatality occur in cases of hepatocellular injury with jaundice. On the other hand, cholestatic DILI cases could be observed with continuation of the suspected causative drug, except if symptoms related to liver injury occur, such as jaundice, elevation of serum bilirubin (more than 3 × ULN), or prolongation of PT-INR (more than 1.5 × ULN). There have been no reports of beneficial therapies except the use of N-acetylcysteine for acetaminophen hepatotoxicity. Corticosteroid therapy may be used in DILI cases with evident hypersensitivity, but it does not have proven benefits[107]. Management of DILI involves prompt withdrawal of the drug suspected to be responsible. A positive de-challenge is a 50% decrease in serum ALT within 8 d of discontinuation of the suspected drug in the hepatocellular type, which is also included in the CIOMS/RUCAM criteria[5,21]. On the other hand, improvement of biliary enzymes after cessation of the suspected drug usually requires a longer period in cholestatic type. However, the time course after cessation of the suspected drug does not always help in early diagnosis and management of DILI, because some patients should be evaluated promptly and managed as suspected DILI on first presentation.

PROPOSAL OF PRACTICAL GUIDELINES FOR DIAGNOSIS AND EARLY TREATMENT OF DILI

Many drugs can cause abnormalities in liver function tests without any symptoms suggestive of liver disease. Preplanned liver function tests should be performed whenever treatment with a new drug is started. In patients with abnormalities in liver function tests without an obvious cause, a careful history, including not only hospital medications but also herbal remedies or supplements, should first be obtained. History taking should also include drug dosage, administration route, previous administration, any concomitant drugs, alcohol consumption, and underlying chronic liver disease and symptoms such as arthralgia. Moreover, family history of adverse drug reactions may be useful for the diagnosis of DILI. On physical examination, patients should be checked for fever, rash, or jaundice. In particular, jaundice should be evaluated carefully,

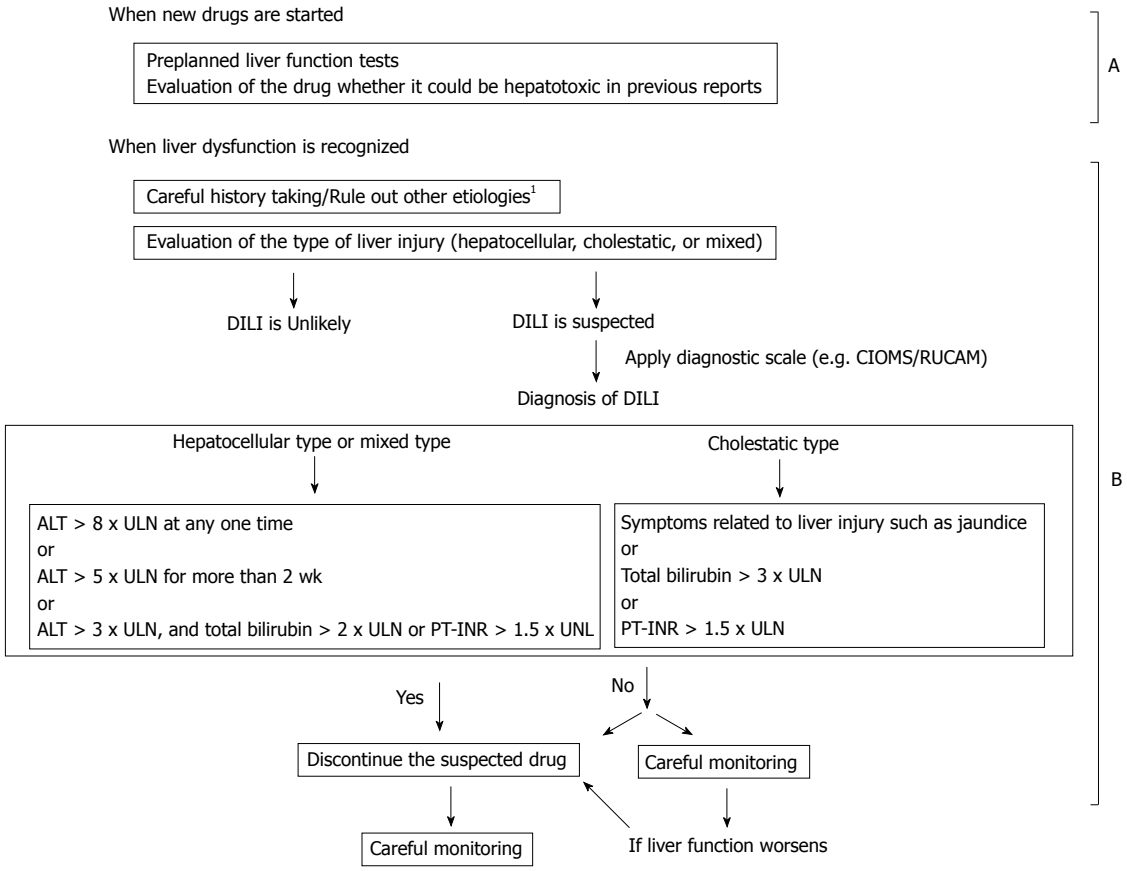

Figure 2 Algorithm for management of DILI. A: When new drugs are started; B: When liver dysfunction is recognized. The type, severity, and causes of liver injury should be assessed promptly. [1]Imaging studies such as ultrasonography should be performed in cases with suspected bile duct disorders.

Table 5 Examinations that should be performed in a patient with suspected DILI

Test	Subjects that can be evaluated
Hematological test[1]	Determination of the type of liver injury (the ratio of ALT and ALP)
Blood count (including eosinophils)	
Biochemical test[1]	
Aspartate aminotransferase (AST)	Possibility (e.g. Increase in eosinophil count, the existence of mixed type liver injury without any biliary disorders on imaging studies, High IgG level (> 2 g/dL) is suspicious of autoimmune hepatitis. Antibodies against hepatitis virus may be false-negative especially in the early phase of infection. Instead, measurement of viral RNA or DNA may be useful for the diagnosis. HDV (requires concomitant HBV infection) and HEV are relatively rare in advanced countries. Although, liver injury caused by EBV or CMV is also relatively rare, young patients with possible DILI should be checked for EBV or CMV).
Alanine aminotransferase (ALT)	
Lactate dehydrogenase	
γ-glutamyl transpeptidase (γ-GTP)	
Alkaline phosphatase (ALP)	
Total bilirubin (including direct and indirect bilirubin)	
Albumin	
Choline esterase (ChE)	
Total cholesterol (Cho)	
Coagulation test[1]	
Prothrombin time international ratio (PT-INR)	
Serological test[1]	
IgG, IgA, IgM	Severity (Marked increase or decrease in white blood cell count, decrease in platelet count. Increase in bilirubin level, decrease in albumin, ChE or Cho levels. Decrease in the ratio of direct/total bilirubin (< 0.67). Prolongation of PT-INR).
Anti-nuclear antibody (ANA)	
Anti-mitochondrial antibody (AMA or M2)	
Viral serology	
IgM anti-HA[1]	
HBsAg[1], IgM-HBc[1], anti-HBc, HBV-DNA	
HCV-Ab[1], HCV-RNA	
HDV-Ab, HDV-DNA	
HEV-Ab, HEV-RNA	
IgM-EBV	
IgM-CMV	
Imaging study	
Ultrasonography (US)[1]	

[1]Tests which should be carried out first. Ig: Immunoglobulin; HA: Hepatitis A; HBsAg: Hepatitis B surface antigen; HBc: Hepatitis B core; HBV: Hepatitis B virus; HCV: Hepatitis C virus; Ab: Antibody; HDV: Hepatitis D virus; HEV: Hepatitis E virus; EBV: Epstein-Barr virus; CMV: Cytomegalovirus.

because it is a sign of severe liver injury indicating the necessity for prompt cessation of the suspected drug. Liver function tests including serum transaminase, ALP, γ-glutamyl transpeptidase, and bilirubin, as well as hematological tests including eosinophil count and coagulation tests should be performed. Classification of the pattern of liver injury should be done as early as possible because clinical course, possible etiologies, and causative drugs are different for each pattern[111]. Other etiologies, such as viral infection, autoimmune liver disease, or biliary disease, should be excluded by serological tests or imaging studies if necessary. DILI cases with severe hepatitis showing elevation of serum bilirubin to more than 3 × ULN may lead to liver failure, and should be treated carefully with referral to the hepatologist after discontinuing all suspected drugs. The list of recommended tests which should be performed in the diagnosis of DILI in patients with liver injury are shown in Table 5. Although accidental readministration of the causative drug may be beneficial for diagnosis of DILI, it may lead to severe liver injury and may even be fatal, and so is not recommended. Moreover, the probability of DILI should also be evaluated using a diagnostic scoring system, such as the CIOMS/RUCAM criteria. However, there is as yet no gold standard set of diagnostic criteria. The initial treatment usually involves withdrawal of the suspected drug. If the causative drug cannot be discontinued because the patient is receiving many drugs or the underlying disease is serious, medications may be continued with careful monitoring. Additional tests, such as the DLST, LMT, or cytokine production test, may be beneficial to identify the causative drug (Figure 2).

CONCLUSION

The spectrum of DILI is both diverse and complex. Although liver injury is often mild and does not require treatment in these patients, DILI may lead to severe hepatitis with a risk of death. Therefore, adequate initial management after achieving an accurate diagnosis is important for physicians. Although the incidence of DILI is reported to be increasing, the precise frequency is difficult to estimate because of the lack of a worldwide monitoring system and the lack of a gold standard for diagnosis. Establishment of a worldwide network for monitoring the adverse events of drugs and a universal diagnostic system for DILI are important for accurate diagnosis, and may lead to better management of DILI.

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