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Drug-induced liver injury 2017: the diagnosis is not easy but always to keep in mind

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Abstract. – A drug-induced liver injury (DILI) is defined as a liver injury caused by exposure to a drug or a non-infectious toxic agent with a variable degree of organ dysfunction. A better understanding of DILI epidemiology has been obtained in recent years with the institution of international registries in the United States and Europe. Despite the advances in the understanding and characterization of the phenomenon, DILI remains an exclusion diagnosis so, probability scores and the analysis of literature reports are useful tools in dealing with a suspected DILI. Idiosyncratic DILI can be considered a relatively rare event but it is one of the leading causes of acute liver failure. Thus, proper management is essential to avoid serious consequences. Here, we present an updated review of diagnostic and classification criteria of DILI. Prognostic tools, and principles of management and therapy have also been briefly discussed.

Key Words
Drug-induced liver injury, DILI, Drug hepatitis, Herbal.

Introduction

Liver often plays a critical role in the metabolism of drugs and xenobiotics, leading to a peculiar risk of toxic effects[1]. Drug-induced liver injury (DILI) is defined as a liver injury caused by exposure to a drug or non-infectious toxic agent, and it is associated with different levels of organ dysfunction[2].

A rise in the alanine-amino-transferase (ALT) and alkaline phosphatase (ALP) level represents a reliable marker of tissue damage[3] while a rise in the total bilirubin (TB), decrease in the plasmatic protein and albumin levels and appearance of coagulopathy (increase in prothrombin time and International Normalized Ratio), are indicative of liver dysfunction. If hepatic adaptive capacity has not exceeded and liver function is not compromised, then the damage may be asymptomatic. On the contrary, the appearance of signs and symptoms such as fatigue, anorexia, nausea, pain in right upper quadrant, dark urine, light stool, and jaundice are certainly indicative of liver dysfunction[4].

For the above-mentioned reasons, biochemical cut-offs for significant liver damage have been proposed in the literature. The first definition of clinically significant liver damage was proposed by a consensus-conference in 1990: ALT or conjugated bilirubin levels elevation, more than two-fold the upper limit of normality (ULN) or the coexistence of aspartate-amino-transferase (AST), ALP and TB elevation, with at least one of them being higher than two times the ULN[2]. In 2001, a consensus conference organized by the American Association for the Study of Liver Diseases (AASLD), in collaboration with the Food and Drug Administration (FDA) and the American pharmaceutics manufacturers and researchers (CDER-PhRMA) defined clinically significant liver damage as the combined elevation of transaminases ≥ 3 x ULN and TB values ≥ 2 x ULN[5]. This statement is consistent with Hyman Zimmerman's observations made in the '70s[6]. Zimmerman noted that the combination of hepatocellular damage (characterized by a predominant elevation of transaminases) and jaundice, without biliary obstruction and ALP elevation, was a particularly severe event, with a mortality range between 10% and 50%. This observation,

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referred to by Dr Robert Temple as "Hy's Law," showed validity over the years and is currently used by the FDA in the evaluation of potential drug-related liver damage[7].

Recently, in an attempt to provide a more uniform criteria for the diagnosis of clinical picture and reporting in the scientific literature, an international DILI Expert Working Group proposed a new definition for drug-induced liver damage: isolated increase of ALT ≥ 5 x ULN or increase of ALT values ≥ 3 x ULN and concomitant increase of TB values ≥ 2 x ULN or increase of ALP values ≥ 2 x ULN and concomitant increase of gamma-glutamyl-transferase (γ-GT) in the absence of any bone disease. In some peculiar cases, such as valproate mitochondrial damage or chronic damages, clinically significant threshold for transaminases and ALP can be lower[8].

From a pharmacological point of view, it is possible to identify two types of DILI: dose-dependent and dose independent or idiosyncratic. Dose-dependent DILI, also known as direct toxicity, is predictable, reproducible and develops with short latency after the consumption of a dose exceeding a known toxic threshold. Damage entity is proportional to administered dose[9]. Idiosyncratic DILI, instead, is unpredictable and usually develops at therapeutic doses. The damage amount is not always proportional to administered dose and the time to damage's onset can vary widely[6,10].

Epidemiology

The proper definition of DILI epidemiology is hard to assess because of difficult diagnosis and signaling issues, with subsequent underestimation of the problem.

Retrospective studies in the United Kingdom and Sweden reported an estimated incidence of 2-3/100,000 per year in the general population[11,12]. Prospective studies in France and Iceland reported an incidence ranging between 13.9-19.1/100,000 per year[13,14].

In these studies, acetaminophen overdose-induced DILI were excluded or represented a minimum percentage, while they are more relevant in the United States[9]. On the other hand, the incidence of idiosyncratic hepatotoxicity seems to be coincident among US and European cohorts[15].

Overall DILI is a rare event even if it is responsible for a high percentage of hospital admission for jaundice, and remains the first cause of acute liver failure (ALF) and ALF-related liver transplantation in the US[16,17]. Under this scenario, the direct toxicity of acetaminophen overdose is overarching. In a prospective US study of 308 ALF cases, idiosyncratic hepatotoxicity was confirmed only in 40 cases (13% of the total), while acetaminophen overdose accounted for 120 cases (39% of the total)[18].

Excluding acetaminophen overdose, DILI is responsible for 7-15% of ALF not only in the US but also in Europe[19,20,21]. Moreover, DILI represents the leading cause of drug withdrawal or prevention of drug marketing[5]. Among hospitalized patients, the reported incidence of drug-induced liver injury is nearly 1%, with the risk being higher when anti-cancer and anti-TBC drugs are involved. But even in this setting of patients, an under-reporting or missed diagnosis could result in a misleading information stating low incidence of DILI[22].

Given the relative rarity of the DILI event, the better understanding of the problem requires the analysis of a high number of cases. For this reason, many epidemiological registers have been created all over the world.

The Drug-Induced Liver Injury Network (DILIN), founded in the US by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), is probably the most trustworthy DILI registries in the world[23].

In Europe, the broader DILI register is the Spanish one, founded in 1994 at Malaga University with actually more than 800 recorded cases[24,25,26].

Both major European registries and USA DILIN agree in reporting the antibiotics as the first class of involved drugs in adverse reactions, with amoxicillin/clavulanic acid the most frequent individual agent[14,23,24,27]. In the above-cited registries, the age of subjects who experimented DILI ranged between 49-53 years (the median age was 55 years in Iceland cohort). In DILIN, LatinDILI, and Iceland cohort, the female sex is predominant (59%, 59%, and 56% respectively) while in the Spanish Registry, there is only a slight prevalence of the male sex (51%).

Interestingly, in the south-east Asian registries, there is a high prevalence of herbs-related DILI, which, in some cases, exceeds 70% of the total cases[28]. This seems to be a different feature compared to Western registers, but in recent years, an increase in herbal and dietary supplements (HDS) hepatotoxicity has been observed in the DILIN prospective network (second most involved class, 16% of the total)[23] (Table I).

Table I. Principal DILI registries and epidemiological records around the world.

Setting	Time period	Country (or countries)	Number of recorded DILI-cases	Comments
DILIN[23]	2004-2013	USA	899	Only idiosyncratic reactions. Most involved classes of drugs: antimicrobial (45%) and HDS (16%). Main single agents involved: amoxicillin/clavulanic acid (10%) and isoniazid (5%). Fatal cases: 10%. Main biochemical pattern of damage at presentation: hepatocellular (54%).
Spanish Registry of Hepato-toxicity[24,26]	1994-2007	Spain	603	Most involved class of drugs: anti-infectious (33%). Most involved single agent: amoxicillin/clavulanic acid (17%). Fatality rates significantly higher among female population ($p<0.01$). Main biochemical pattern of damage at presentation: hepatocellular (55%).
LatinDILIN[27]	2011-2015	Argentina, Uruguay, Chile, Mexico, Paraguay, Venezuela, Ecuador, Brazil, and Peru	206	Most involved classes of drugs: anti-infective, musculoskeletal agents and sex hormones. Most involved single agents: amoxicillin/clavulanic acid (10%) and diclofenac (6%). Fatal cases: 4,6%. Main biochemical pattern of damage at presentation: hepatocellular (54%).
Population-based study of DILI in Iceland[14]	2010-2012	Iceland	96	Crude annual incidence of idiosyncratic DILI among the population of Iceland: 19.1/100,000. Most involved classes of drugs: antibiotics (37%) and immunosuppressant (10%). Most involved single agents: amoxicillin/clavulanic acid (22%) and diclofenac (6%). Fatal cases: 1%.
Korean prospective nationwide study of DILI[28]	2005-2007	South-Korea	371	Most involved class of drugs: HDS (73%). Main biochemical pattern of damage at presentation: hepatocellular (78%). Fatal cases: 1.5%.

Drug Induced Liver Injury (DILI), Drug Induced Liver Injury Network (DILIN).

Pattern of damage

The identification of damage pattern is useful not only for classification but also for diagnostic, prognostic and reporting aspects, with the purpose of data homogenization for Drug regulatory agencies and scientific communication.

The biochemical pattern of liver damage is defined by the ratio ALT/ULN / ALP/ULN at presentation, the so-called "R ratio". An $R \geq 5$ identifies the hepatocellular pattern of injury; $R \leq 2$ identifies the cholestatic pattern, while an R between 2 and 5 defines the mixed pattern. If ALT>2 ULN and ALP is normal, the damage pattern is considered as hepatocellular[29]. Conventionally, ALT and ALP values should be acquired on the same day or no later than 48 hours apart from each other[30].

When ALT or ALP are unavailable, AST and γ-GT could be used with good agreement in the hepatocellular pattern of damage (94-96%)[31], even if their reliability is not completely defined.

When an alteration in liver enzymes pre-exists to DILI, it is possible to use as pre-damage reference value the previous mean levels of ALT and ALP[32].

In addition to the above biochemical patterns of liver injury, some clinical-laboratory phenotypes have been proposed to better define the disease. They include acute hepatic necrosis, acute hepatitis, cholestatic hepatitis, mixed hep-

atitis, enzyme elevations without jaundice, bland cholestasis, hepatic steatosis and lactic acidosis, non-alcoholic fatty liver, chronic hepatitis, the sinusoidal obstruction syndrome (or vein-occlusive disease), nodular regenerative hyperplasia and the development of hepatic neoplasia-like adenomas and hepato-carcinomas[33].

In addition to the biochemical pattern, a histological pattern of damage may be identified. Recently, the DILIN reported a series of possible histological patterns in a prospective systematic analysis of 249 biopsies performed on patients with suspected DILI: 1) acute hepatitis; 2) chronic hepatitis; 3) acute cholestasis; 4) chronic cholestasis; 5) cholestatic hepatitis; 6) granulomatous changes; 7) steatosis; 8) steatohepatitis; 9) coagulative/confluent necrosis; 10) massive/sub-massive necrosis; 11) vascular injury; 12) hepatocellular alteration; 13) nodular regenerative hyperplasia; 14) mixed injury; 15) unclassifiable injury; 16) minimal nonspecific changes; 17) normality (Table II).

Nevertheless, 206 of the analyzed biopsies (83% of the total), had just one of the five dominant histological patterns: acute hepatitis, chronic hepatitis, acute cholestasis, chronic cholestasis and cholestatic hepatitis. The observed histological patterns were strictly connected with the involved drugs, strengthening the concept of "*histological signature*": a specific drug causes specific tissue modifications[34].

The concept of "*drug signature"* has also been strongly validated for other features of DILI such as severity, latency, and biochemical pattern[35].

Table II. Histological patterns of liver damage[34].

Dominant pattern of damage	Prevalence
Acute cholestasis	High
Acute hepatitis	High
Cholestatic hepatitis	High
Chronic cholestasis	High
Chronic hepatitis	High
Coagulative/confluent necrosis	Low
Fibrosis/Cirrhosis	Low
Granulomatous changes	Low
Hepatocellular alteration	Low
Massive/sub-massive necrosis	Low
Minimal nonspecific changes	Low
Mixed injury	Low
Nodular regenerative hyperplasia	Low
Normality	Low
Steatohepatitis	Low
Steatosis	Low
Unclassifiable injury	Low
Vascular injury	Low

Diagnosis

The diagnosis of DILI is a diagnosis of exclusion. Clinical history, time of drug exposure and course of liver damage are crucial points in the evaluation of subjects with suspected drug-induced liver injury. Usually, DILI manifestations are highlighted in the six months following the start of the involved drug[29], although there are some exceptions[24]. The key aspect in the assessment of a suspected DILI is the exclusion of other causes of DILI, and the biochemical pattern of presentation could help in the diagnostic process[36] (Table III).

According to the American College of Gastroenterology (AGA) guidelines[29], in hepatocellular liver injury, the first condition to be excluded is acute viral hepatitis (HAV, HBV, HCV, HEV, CMV, EBV, and HSV), autoimmune hepatitis (AIH), vascular liver diseases (Budd-Chiari syndrome, ischemic liver injury) and Wilson's disease[37]. Regarding AIH, it should be noted that some drugs, such as minocycline and nitrofurantoin, can induce a peculiar form of DILI, very similar to that of idiopathic AIH[38]; therefore, a differential diagnosis can be difficult. According to AASLD guidelines, these difficult cases remain an indication for liver biopsy[39].

In the cholestatic pattern, the first condition to be excluded is a biliary obstruction. Other conditions to take into account include total parental nutrition[40] and sepsis[41]. Biliary autoimmune diseases such as primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) can be investigated by searching for specific autoantibodies (AMA and p-ANCA respectively) and with liver biopsy in PBC or proper imaging techniques in the case of PSC[42,43].

Liver imaging can also reveal infiltrative hepatic diseases[44] and fatty liver diseases (NAFLD/NASH)[45].

Differential diagnosis also includes hemochromatosis and α-1-antitrypsin deficiency, which can be excluded assessing iron metabolism parameters and serum enzymatic activity, respectively[29].

Once the other possible causes of damage are excluded, it is necessary to define the causal link between the involved drug and the observed liver injury.

Among the parameters considered in causality assessment, particular attention should be paid in defining the time criterion (drug administration must precede the development of liver injury), the de-challenge (improvement of liver damage

Table III. Biochemical pattern of liver damage and related drugs according to major registries[4,48].

Hepatocellular	Cholestatic	Mixed
Acetaminophen	Amoxicillin-clavulanic acid	Allopurinol
Allopurinol	Anabolic steroids	Azathioprine
Clindamycin	Captopril	Carbamazepine
Clopidogrel	Cefazolin	Chlorpromazine
Disulfiram	Chlorpromazine	Clindamycin
Fluoxetine	Cyproheptadine	Cyproheptadine
Flutamide	Enalapril	Doxycycline
Herbals	Estrogens	Methimazole
Imatinib	Griseofulvin	Mycophenolate mofetil
Interferon alpha and beta	Macrolides	Phenobarbital
Irbesartan	Methimazole	Phenytoin
Isoniazid	Oral contraceptives	Sulfonamides
Ketoconazole	Sulfonylureas	Trimethoprim-sulfamethoxazole
Lamotrigine	Terbinafine	Verapamil
Levofloxacin	Ticlopidine	
Lisinopril	Trimethoprim-sulfamethoxazole	
Losartan	Verapamil	
Methotrexate		
Methyldopa		
Minocycline		
Mycophenolate mofetil		
Nitrofurantoin		
NSAIDs		
Omeprazole		
Pyrazinamide		
Propylthiouracil		
Rifampin		
Valproic acid		

after drug discontinuation) and the re-challenge[46] (new presentation of the damage, usually with short latency and greater magnitude, at drug re-administration).

As the time-to-onset of DILI after drug administration can vary widely, from few days to even more than one year, detecting the implicated drug can be very difficult, especially in polypharmacotherapy[4]. In these cases, the research of the scientific literature of cases reports or similar clinical experiences can help to make the correct diagnosis[47]. LiverTox[48], a free online database of more than 650 potentially hepato-toxic drugs, may be consulted for free.

Many scores systems have been proposed for causality assessment of DILI. Among others, Roussel Uclaf Causality Assessment Method (RUCAM), Maria and Victorino scale (M&V) and the Naranjo probability scale are the most used and widely accepted.

RUCAM is probably the most accurate and reproducible one. It considers the biochemical pattern of damage, the onset time and the course of damage, risk factors, polypharmacotherapy, literature data about hepatotoxicity of the suspected drug and the effect of the "*re-challenge"* when applied[30,49].

M&V was developed in order to improve RUCAM performance. When compared to RUCAM, it appears to be easier, even if less accurate[50].

Naranjo scale is not specific to hepatic adverse reactions but is the most rapid to use in the assessment of adverse drug reactions[51,52].

The above-mentioned scores have been proposed with the aim of guaranteeing an objective assessment of causality in the case of adverse drug reactions, but the most used method remains "expert opinion". In DILIN registry, three experts independently review suspected DILI cases and the probability category is accepted if there is a full matching of assessments, otherwise experts meet to define the most appropriate probability. The DILIN prospective study compared RUCAM score and expert opinion assessment. Expert evaluations demonstrated higher agreement rates than RUCAM score but both showed a considerable inter-observer variability[53] (Table IV).

Table IV. Causality assessment methods to support the diagnosis of DILI.

Hepatocellular	Cholestatic	Mixed
Roussel Uclaf Causality Assessment Method (RUCAM)[30]	7 analyzed aspects: -Time to damage onset -Effect of drug discontinuation -Risk factors -Concomitant medications -Potential other causes of liver injury -Known hepatotoxicity of the implicated drug -Effect of rechallenge	5 probability levels: -Highly probable -Probable -Possible -Not likely -Excluded
Maria and Victorino scale (M&V)[50]	5 analyzed aspects: -Time to damage onset -Potential other causes of liver injury -Extrahepatic manifestations -Known hepatotoxicity of the implicated drug -Effect of rechallenge	5 probability levels: -Definite -Probable -Possible -Not likely -Excluded
Naranjo scale[51]	10 questions answered as either Yes/No/Don't know: -Previous conclusive reports of the reaction? -Adverse reaction onset after drug administration? -Adverse reaction improvement after drug discontinuation or antagonist administration? -Adverse reaction reappearance upon drug re-administration? -Are there other possible cause for the reaction? -Adverse reaction reappearance after placebo administration? -Drug detected in blood at toxic concentrations? -Worsening of the reaction at increasing doses or improvement upon decreasing doses? -Previous reactions to the drug or related agents? -Adverse reaction confirmed by any other evidence?	4 probability levels: -Definite -Probable -Possible -Doubtful
Drug Induced Liver Injury Network (DILIN) causality assessment method[53]	Case evaluation by three independent experts based on history, clinical and laboratory findings. Assessment accepted if there is a complete agreement among the three expert reviewers. In case of disagreement, reviewers meet to reconcile the differences and reach a final single score.	5 probability levels: -Definite -Highly likely -Probable -Possible -Unlikely
Expert opinion	Subjective judgement of the association between the involved drug and the adverse event by one or more experts	

Recently, Bjornsson and Hoofnagle proposed to add to the causality assessment the analysis of the number of literature reports for the suspected drug. They classified drugs in the LiverTox database in five categories according to the number of published case-reports. Of 671 investigated drugs, 318 (47%) had no convincing reports of hepatotoxicity. They found that pharmacological agents with the higher number of published reports had at least one instance of a fatal outcome or a re-challenge. These authors have proposed a new causality assessment method based on RUCAM score that would be able to give a different probability weight based on the number of cases-reports[47].

Therefore, it is clear that new and more reliable tools are needed to improve the final DILI diagnosis. Experimental studies on the use of new markers of liver injury, such as *high-mobility group box 1 protein*, the keratine-18 and the miRNA-122, are ongoing[3]. Several studies have been conducted with the aim to identify genetic polymorphism predisposing to DILI, but at present, robust data are lacking, with the exception of flucloxacillin-induced liver injury[54,55]. HLA-B*5701 allele is associated with an 80.6 fold increase (p=9x10^{-19}) of risk of flucloxacillin hepatotoxicity. This polymorphism has a low positive predictive value (0.12%) and a high negative predictive value (99.99%). For these reasons,

HLA-B*5701 polymorphism could be useful in the differential diagnosis of cholestasis in subjects exposed to flucloxacillin but a positive test should not influence drug prescription[56].

Liver toxicity induced by herbal and dietary supplements (HDS)

In 1998, the World Health Organization estimated that 80% of the world population preferentially used herbs for therapeutic purposes[57]. This is traditionally a feature of some regions of the world, mainly in the east or Africa, but in recent years, the use of such products has significantly increased in the Western countries as well[58,59]. Herbal products can have pharmacological properties even if they're not clearly recognized as medicines so, they can have beneficial but also toxic and adverse effects. As for drugs, the herbal liver toxicity can be direct or idiosyncratic. Herb-herb, herb-drug interactions and toxic effects from contaminants are also to be taken into account. In fact, adulteration of herbal products with traditional drugs, heavy metals, microbes or pesticides has been reported in literature[60].

The English expression "herbal and dietary supplements" (HDS), refers not only to herbal products, but also to dietary supplements containing vitamins, minerals, amino-acids, proteins, enzymes, gland or organic tissues, chemically synthetized molecules and even illicit anabolyzing steroids[61].

In many countries, the regulation about composition, dosage, and quality of HDS is often lacking or incomplete so manufacturers are not always obliged to declare an exhaustive analytical description of the marketed products. For these reasons, safety and effectiveness of HDS is not always ensured, and occurrence of toxicity is, therefore, not a rare event[62,63,64].

Based on the DILIN registry, HDS are responsible for 16% of the observed DILI. In 76% of these DILI (otherwise referenced as HDSILI) was attributed to a mix of different active principles so it is hard to identify the single active substance responsible for the toxic event[60].

The approach to HDSILI should include a detailed patient medical history focused on identifying the assumed product, the purchasing methods, preparation, storage, and intake. When possible, the visual analysis of the product and the laboratory analysis should be obtained. After proper analysis of the implicated product, confounding factors, such as drug interactions, presence of contaminants, pre-existing diseases and inadequate product preparation, must be considered[60].

Reports of HDSILI are heterogeneous and of extremely variable quality mainly because of the difficulties in case definition and characterization. A lot of herbs from Chinese, Indian and Korean traditional medicine such as ephedra sinica (ma huang)[65], larrea tridentata (chaparral)[66], germander[67], black cohosh[68], European mistletoe[69], pennyroyal oil[70], some flower plants containing pyrrolizidine alkaloids[71], green tea extract[72], kratom (mitragyna speciosa), roman absinthe (artemisia herba alba), aegelina (aegle marmelos), and garcinia cambogia, have been reported to cause liver injury[73,74].

Diagnostic and therapeutic approach to HDSILI is not different from conventional DILI but expert opinion can assure better results than RUCAM in causality assessment[29].

Prognosis

DILI outcome is generally favorable, with 90% of recoveries in case of drug discontinuation[29], but a not so negligible percentage of subjects can experience adverse outcomes such as ALF or chronic liver disease.

Female sex, older age, pre-existing liver disease, alcohol abuse, hepatocellular biochemical pattern and some genetic determinants are associated with a more severe course of DILI and adverse outcome (death or transplantation)[75,76], but risk factors can vary according to the involved agents. In subjects who experiment a re-challenge, in any case unintentional, the outcome can be worse[46].

ALF is defined by the presence of coagulopathy and encephalopathy in subjects without liver cirrhosis and with an illness of <26 weeks' duration. It is associated with a mortality rate of 60-80% without liver transplantation[77,78,79]. Among drug-induced ALF, acetaminophen overdose appears to have a better prognosis than idiosyncratic reactions[36]. In DILIN and Spanish Registry, fatal outcome (death out of need for liver transplantation) accounted for 10% and 7% respectively[23,24]. In severely adverse reaction, the major challenge is the early identification of the subject whose condition will progress to ALF and who will require orthotopic liver transplantation, which is the best therapeutic choice in subjects who don't have spontaneous recovery[80].

In acetaminophen overdose, the Rumack-Matthew monogram, combining plasmatic drug levels and time passed since assumption, could be a valid instrument in patients' monitoring[81]. Furthermore, the *Model for Acetaminophen-induced Liver Damage,* that considers ALT, AST, INR, and creatinine, showed a 100% sensitivity and a 91% specificity in predicting mortality[82].

Prognostic assessment in idiosyncratic DILI can be more difficult. The MELD (Model for End-Stage Liver Disease) score and plasmatic hemoglobin could be used as predictors of short-term outcome and is therefore needed for OLT[21,83].

King's College Criteria (KCC) were constructed in 1989 from the retrospective analysis of a cohort of 588 patients with acute liver failure. In acetaminophen-induced ALF, arterial pH, prothrombin time and creatinine significantly correlated with prognosis while in non-acetaminophen-induced ALF, static variables such as etiology (non A, non B hepatitis or DILI), age and duration of jaundice before the onset of encephalopathy and two dynamic variables, such as bilirubin and prothrombin time, correlated with prognosis[84].

In a prospective study conducted in the US, KCC were tested in 275 patients with acetaminophen-induced toxic ALF. KCC were fulfilled in only 40 subjects, of whom 19 died and 6 underwent transplantation. This study confirmed a good specificity of the criteria in predicting a fatal outcome (92%) but adverse outcome was also high among patients who did not meet the KCC, resulting in a low sensitivity (26%). In the same study, the Acute Physiologic and Chronic Health Assessment II (APACHE II) appeared to be more sensitive (68%) but slightly less specific (87%) than KCC in predicting patients' transplant-free survival[85].

McPhail et al[86] in a recent meta-analysis evaluated the performance of KCC and MELD score in both acetaminophen and non-acetaminophen induced ALF. The overall diagnostic accuracies of KCC and MELD were substantially comparable even if KCC appeared to be less sensitive while MELD score was less specific. Neither of these scores appeared to be optimal but KCC are probably more reliable in acetaminophen-induced ALF while MELD score could be useful in prognostic evaluation of non-acetaminophen-induced ALF.

In acetaminophen overdose, the *Sequential Organ Failure Assessment* (SOFA score) has shown to perform better than MELD, APACHE II and *KCC* in selecting liver transplant candidates[87].

The combination of MELD score and serum apoptotic markers, such as caspase-cleaved CK-18 or intact product, by means of M-30 or M-65 ELISAs[88] or the combination of such apoptotic products with clinical parameters (coma grade, INR, bilirubin and phosphorus levels)[89] appears to predict the ALF outcome better than classical scores such as Kings College Criteria and MELD. These methods represent an attractive prospective but their use is limited by the difficulty of obtaining such determinations routinely.

Robles-Diaz et al[90], recently proposed a new index to predict ALF in DILI. They integrated the Hy's rule with the "new R ratio" (nR), obtained by the ratio of the higher among AST and ALT/ALP, both normalized for ULN. A positive Hy's rule and an nR≥ 5 at presentation showed a sensitivity of 90% and a specificity of 63% in predicting the risk of ALF.

In some cases, DILI may progress to chronic injury. In DILIN, chronic liver injury is intended as a persistent increase in liver enzymes or histological and radiological evidence of liver damage, lasting six months or more[91]. Using this cut-off, the prevalence of chronic damage is 15-20% and cholestatic DILI seems to have a higher risk of chronicity[92]. Recently, a period of 12 months has been proposed for the definition of chronic damage. With this longer cut-off, the prevalence of chronic liver damage is 10% and cholestatic DILI does not show an increased risk of chronicity but only a slower resolution[25]. Risk factors for development of chronic DILI are advanced age, female sex, and severity of the acute DILI[93]. Biochemical predictors of chronic damage development are ALP > 1.1 x ULN and a TB > 2.8 x ULN at the second month damage onset[25].

Chronic DILI can present an anatomo-pathologic evaluation with different patterns such as cirrhosis, steatosis[94], steatohepatitis[95], nodular regenerative hyperplasia[96], peliosis[97] and vanishing bile duct syndrome[98,99].

Damage monitoring and therapy

Routine monitoring of liver enzymes has not shown favorable costs/benefits ratio in preventing the liver from severe adverse events[15]. Serum determination of the involved drug and its metabolites, instead, can be useful in the prevention and management of some kinds of direct hepatotoxicity[9,100].

The development of signs and symptoms of liver damage always deserve a comprehensive hepatological evaluation. In some cases, patient education can be useful in the early recognition of signs and symptoms of DILI[101,102].

The main treatment for DILI is discontinuation of the involved drug. This can determinate clinical and biochemical improvement and prevent severe liver damage. To avoid useless discontinuation of needed therapies, clinically significant DILI should be distinguished from tolerance phenomenon and adaptive response[103]. The transient mild increase of liver enzymes, in fact, does not necessarily imply liver damage. To distinguish real DILI from adaptive response and tolerance, FDA in 2009 suggested to perform a laboratory monitoring if ALT or AST > 3 x ULN. Suspected drug must be discontinued when ALT or AST > 8 x ULN, ALT or AST > 5 x ULN for more than two weeks, and ALT or AST > 3 x ULN with TB > 2 x ULN or INR > 1.5 and ALT or AST > 3 x ULN with hypersensitivity symptoms and signs[104].

Specific treatments for DILI are scarce. N-acetylcysteine (NAC) is the consolidated antidote in case of acetaminophen overdose[9,105]. NAC administration can also increase the probability of transplant-free survival in adults diagnosed with idiosyncratic DILI due to other causes[106,107].

Corticosteroids can be used in DILI with clinical and laboratory manifestations of hyper-sensitivity and in DILI-induced autoimmune hepatitis[108,38]. Antihistamines such as hydroxyzine and diphenhydramine can be useful as a symptomatic treatment for itching in cholestatic DILI, eventually in association with cholestyramine[109]. The latter can have a specific indication for treatment of the leflunomide-induced liver injury[110]. L-carnitine is recommended in the treatment of valproate-induced direct hepatotoxicity[111,112] while folic acid is used to reduce methotrexate toxicity[113].

Ursodeoxycholic acid is vastly used to treat cholestatic DILI but its efficacy is uncertain[114].

OLT is the rescue treatment for DILI-induced ALF but proper timing and organ availability are critical criteria. In this scenario, patients with cholestatic DILI seem to have such an advantage because of its slower evolution than hepatocellular DILI[29]. MARS (*Molecular Adsorbent Recirculation System*) therapy and other extracorporeal detoxification system have been proposed over the years as supportive therapies in patients awaiting liver transplantation, but their efficacy and cost/benefit is still under debate[115,116].

Conclusions

DILI is a relatively rare event, but it can have serious consequences in some cases. The actual epidemiological dimension of DILI is still affected by the absence of general registers in most countries and an under-reporting attitude. Nevertheless, the presence of a few national registries such as the Swedish, French and the Spanish registry may help in the understanding of the problem. Collaborative prospective studies on large series with molecular and genetic analysis will allow a better understanding of the pathogenic factors and mechanisms of injury in the future.

The future challenge is the identification of individual predisposing factors that could allow a better customization of drug therapy in order to reduce the incidence of severe DILI.

The creation of international consortia for the registry and the study of individual predispositions to DILI is desirable and, today, thanks to the organizational efforts of some pilot countries, a European consortium with these purposes is emerging[117].

Conflict-of-interest statement

Marrone M, Vaccaro FG, Biolato M, Miele L, Liguori A, Araneo C, Ponziani FR, Mores N, Gasbarrini A and Grieco A declare no conflict of interest related to this publication.

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