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Drug-induced liver injury: a clinical update

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Abstract

Purpose of review—To gather new and important data published on idiosyncratic drug-induced liver injury (DILI) over the past 2 years in the peer-reviewed literature. Clinical studies focusing on mechanisms of injury, clinical evaluation and prognosis will be reviewed.

Recent findings—The most common drugs leading to DILI in the United States are antibiotics, central nervous system agents, herbal/dietary supplements and immunomodulatory agents. Hepatocellular type of DILI is more common in younger patients, whereas cholestatic pattern increases with older age. Certain human leukocyte antigen genotype increases the likelihood of flucloxacillin-induced liver injury. Idiosyncratic DILI was shown to have an important dose-dependency and drugs with extensive hepatic metabolism are associated with higher frequency of DILI. Chronic DILI may occur, but development of clinically important liver injury after severe DILI is rare. *N*-acetylcysteine seems to be beneficial for patients with acute liver failure caused by medications or herbal agents.

Keywords

diagnosis; drug-induced liver injury; hepatotoxicity; natural history

Introduction

Drug-related hepatotoxicity is a serious health problem, with broad implications for patients, healthcare providers, the pharmaceutical industry and governmental regulatory agencies. Drug-induced liver injury (DILI), whether dose-related as with acetaminophen or idiosyncratic, is the most common cause of acute liver failure in the United States [1]. In addition, DILI is the most common cause of aborted development or withdrawal of otherwise promising drugs [2].

The risk factors, pathogenesis and outcomes of idiosyncratic DILI are poorly understood. The study of DILI is confounded by the heterogeneity of its clinical presentation and course of injury, ranging from asymptomatic transient elevations in liver enzymes to liver failure and in rare cases chronic liver disease; the delay in establishing its diagnosis as it requires exclusion of other causes of liver injury; the lack of standardized criteria or specific ‘gold standard’ diagnostic tests for DILI; and underreporting of cases of DILI or their final outcomes. This paper reviews recent publications on this topic over the past 2 years.

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Epidemiology

The epidemiology of DILI is influenced by geographic and cultural factors, as well as by variable study designs and definitions. In western countries, acetaminophen is the leading cause of DILI and it is well known to be dose-related or intrinsic in nature. Idiosyncratic DILI, however, is a rare and unpredictable event and may not be identified in preclinical or clinical testing. DILI in the case of any single drug is thought to occur approximately in one per 10 000–100 000 treated patients. The variable incidence of DILI in a number of large retrospective studies underscores the challenges in diagnosing DILI and the need for prospective data.

The Drug Induced Liver Injury Network (DILIN), a federally funded consortium of several centers in the United States, recently reported the preliminary results of its prospective study [3••]. It consisted of 300 patients with suspected DILI enrolled prospectively over a 3-year period between 2004 and 2007. This study excluded patients with acetaminophen-related hepatotoxicity and patients with preexisting autoimmune liver diseases such as primary sclerosing cholangitis (PSC) and primary biliary cirrhosis (PBC). Patient ages were 2–18 years in 7% of cases, 18–65 in 75% and more than 65 in 18%, whereas 60% were females. Similar to prior registry reports, a single drug was most commonly implicated, accounting for 73% of DILI cases. However, multiple drugs were implicated in 18% of cases and herbal or dietary supplements in 9% of cases, which were higher than the rates reported by the prospective Spanish registry study [4]. This may be potentially related to greater polypharmacy and the use of herbal or dietary supplements in the US population. More than 100 different compounds were implicated in this DILIN prospective study, but antimicrobials (45.5%) and central nervous system agents (15%) were the two most common classes of agents implicated. Less common classes included immunomodulatory agents (5.5%), analgesics (5%), antihypertensive agents (5%), antineoplastic agents (4%) and lipid-lowering agents (3.4%). The most common single causative agents were amoxicillin–clavulanate in 23 cases, and trimethoprim–sulfamethaxazole, nitrofurantoin and isoniazid in 13 cases each.

The use of herbal or dietary supplements, when implicated in DILI, was intended for muscle building or weight loss in 60% of those cases [3••]. The importance of these supplements as a cause of DILI is further underscored by a retrospective Japanese study, in which 10% of 879 cases of single agent DILI from 1997 to 2006 were attributed to dietary supplements and 7% to Chinese herbal drugs [5]. These rates were significantly higher than those reported in a 1998–1999 study of 0.7 and 4.7%, respectively [6]. Symptomatic DILI was more common with Chinese herbals, which may account for increased reporting of those cases, whereas DILI related to dietary supplements was less frequently symptomatic and may be the result of increased use of these products by the Japanese population. Taken together, these data may reflect evolving cultural trends and impact of obesity within the sphere of geographic variability influencing the incidence and etiology of DILI.

Risk factors

Susceptibility to DILI is thought to be influenced by certain patient characteristics, predominantly age and sex, though there have been insufficient data to define increased risk in any given patient subpopulation. In addition to any effect of age on physiologic reserves, the influence of age may be multifactorial as it relates to the number and type of medications and underlying comorbidities. In a recent Japanese study of 396 hospitalized patients with acute hepatitis (142 for DILI), age at least 65 was associated with a higher proportion of patients with DILI (62 vs. 26%, $P < 0.001$) [7]. Age at least 75 was associated with more frequent use of concomitant drugs and a cholestatic injury pattern.

Women are thought to have greater susceptibility to DILI in several previous studies. Fulminant liver failure and liver transplantation due to DILI were more common in women in a recent analysis of the Spanish registry data [8•]. This finding was not corroborated by the DILIN study, which revealed no difference in the proportion of female sex in those with severe (59%) or mild-to-moderate (57%) DILI [3••]. However, the data from both studies appear to suggest an association of age and female sex with the pattern of liver injury. In the DILIN prospective study, compared to mixed and cholestatic pattern of DILI, hepatocellular DILI had lower mean age (mean age 44 years in the hepatocellular group vs. 54 years in two other groups, $P < 0.0001$) and higher proportion of female sex (65% in the hepatocellular group vs. 57 and 50% in other two groups, $P = 0.09$) [3••]. In the Spanish registry, hepatocellular DILI was more common in women under the age of 60 years (1.2-fold increase over men), whereas cholestatic pattern was more common in men over the age of 60 [8•].

Novel findings from the DILIN study indicate that diabetes mellitus and alcohol use were significantly associated with DILI severity [3••]. In a multivariate analysis that included these factors, age, sex, race, duration of drug exposure and pattern of liver injury, the only significant predictors of DILI severity were diabetes mellitus (odds ratio 2.6) and alcohol use in the preceding 12 months (odds ratio 0.33). A protective effect of alcohol was surprising as alcohol use increased the probability score of DILI by a causality algorithm used by this and other recent studies. However, data are relatively scanty to support the inclusion of alcohol consumption as a risk factor in the Roussel Clef Causality Assessment Model (RUCAM) causality instrument [9•].

There has been a recent surge of genetic studies in the field of DILI. The association between *N*-acetyltransferase 2 (NAT-2) genotype and an increased risk for isoniazid hepatotoxicity was noted in a reproducible fashion [10]. A UK genome-wide association study of 51 cases of flucloxacillin-related DILI and 282 matched controls identified human leukocyte antigen (HLA)-B*5701 genotype as a major determinant of flucloxacillin DILI (odds ratio 80.6, $P = 9 \times 10^{-19}$) [11••]. Interestingly this genotype is more common in northern Europe than Asia or Africa (www.allelefrequencies.net/); therefore, race or ethnicity may increase susceptibility to DILI with certain agents, although current data do not allow meaningful epidemiologic analysis.

Causality assessment

In the absence of a ‘gold standard’ diagnostic test for DILI, causality is established based on the clinical history, chronology of exposure and injury, exclusion of competing etiologies and subjective assessment based on clinical experience and published data wherever available. Causality assessment algorithms have been developed by hepatotoxicity experts to measure the strength of association between suspected DILI and an implicated agent [12]. Validation of such instruments is critical to standardizing their clinical and research application in DILI. The reliability of RUCAM, an instrument used by both the DILIN and the Spanish registry studies, was tested by researchers from DILIN in cases of well defined DILI [13•]. Clinical summaries of 40 selected cases of clinically well defined DILI were reviewed by the enrolling site primary investigator and two external investigators on two occasions at least 5 months apart. Cases were independently scored using RUCAM on both occasions, and the scores were compared for interobserver and test–retest reliability. Enrolling investigator mean RUCAM scores (7.2 ± 0.5) were higher than external investigator scores [(6.4 ± 0.5), $P = 0.007$]. Overall interobserver reliability was 0.45 and test–retest reliability was 0.54, whereas test–retest reliability in enrolling site investigators only improved to 0.65. Although these results raise concerns about the validity of this algorithm, analyzing scores by five categories of highly probable (>8), probable (6–8),

possible (3–5), unlikely (1–2) and excluded (≤0), improved reliability marginally. At present, there are no superior algorithms, and current studies combine these instruments with opinions of expert panels by design [3••,8•]. Modification of existing algorithms or development of novel instruments is needed to establish causality more robustly.

The exclusion of competing etiologies of liver disease is integral to the evaluation of suspected DILI. Interestingly, a small number of patients in the DILIN study were diagnosed with hepatitis C infection, detectable only by RNA in some cases, with no obvious risk factors, emphasizing the need for hepatitis C RNA testing in the course of evaluation [3••].

Drug properties as risk factors for drug-induced liver injury

In general, idiosyncratic DILI is considered to be unpredictable as well as dose-independent [14]. However, it has been suggested that there is dose-dependency for some drugs [15]. It was suggested by Uetrecht [16] that most drugs associated with severe liver injury were prescribed at a daily dose greater than 50 mg, suggesting some dose-dependency at least for severe cases of DILI. This hypothesis that idiosyncratic DILI may have a component of dose-dependency was tested in a recent study [17••]. By using two pharmaceutical databases, the relationship between daily doses of commonly prescribed medications in the United States and reported frequency of their hepatic adverse events was examined. Furthermore, serious DILI cases, that is, DILI with concomitant jaundice reported to Swedish authorities, were examined for any signals supporting the relationship between daily dose and the idiosyncratic DILI, based on patients' data reported in a previous study [18]. Drugs were categorized into the following groups: 10 mg/day or less, 11–49 mg/day and at least 50 mg/day. Among US prescription medications, a statistically significant relationship was observed between daily dose of oral medicines and reports of liver failure, liver transplantation and death caused by DILI but not of alanine aminotransferase (ALT) more than three times upper limit of normal (ULN) or jaundice. Of approximately 600 Swedish cases, only 9% belonged to the 10 mg/day or less group, 14% to the 11–49 mg/day group and almost 80% to the at least 50 mg/day group. Authors reanalyzed the previously reported cases of acute liver failure caused by DILI requiring liver transplantation in the United States [19] and found that 90% of cases belonged to the at least 50 mg/day group. Thus, this study consisting of different datasets supports a relationship between the daily dose of an oral medication and its propensity to cause serious liver injury. The results of this study were recently confirmed by data from the Spanish registry of hepatotoxicity [8•]. Among approximately 600 cases, 77% were receiving daily doses of at least 50 mg/day, which was exactly the same percentage that was found in the Swedish dataset in the study by Lammert *et al*. [17••]. It is unknown whether the classes of agents overrepresented in these two series [e.g., antibacterials and nonsteroidal antiinflammatory drugs (NSAIDs)] are more hepatotoxic because their usual daily dose was at least 50 mg/day or whether the association between daily dose and DILI is driven by the enrichment of these classes of agents in the at least 50 mg/day group.

Regardless, this purported relationship between daily dose and idiosyncratic DILI supports the reactive meta-bolite theory for the pathogenesis of idiosyncratic DILI. Further support for that hypothesis came from another recently published group by the Indiana group [20••]. This study examined the relationship between hepatic metabolism of oral medications and idiosyncratic DILI. By using two pharmaceutical databases, the metabolism characteristics of approximately 200 most prescribed drugs in the United States were analyzed. Compounds with more than 50% hepatic metabolism were characterized as those with significant hepatic metabolism. Compared with compounds with lesser hepatic metabolism, compounds belonging to the significant metabolism group had significantly higher frequency of ALT more than three times ULN, liver failure and fatal DILI but not of jaundice or liver

transplantation. Twelve compounds with no hepatic metabolism had no reports of liver failure, liver transplantation or fatal DILI. Compared with drugs without biliary excretion, compounds with biliary excretion had significantly higher frequency of jaundice. Furthermore, an additive effect of daily dose and hepatic metabolism was observed. Thus, compounds with more than 50% hepatic metabolism and also given at a dose of more than 50 mg/day had the highest risk of hepatotoxicity compared with other groups. Although this study is a database study, with retrospective collection data with several limitations, its results are of importance. Supporting data for the reactive metabolite have been limited and if reproduced by others might facilitate the development of safer medications.

More recently, Suzuki *et al*. [21] found that certain coadministered medications may adversely influence the outcome of acetaminophen-associated liver injury. Data from more than 6000 cases with acetaminophen-induced liver injury and fatal vs. nonfatal cases were compared with a particular focus on concomitant use of nine drug classes using multiple regression analyses. Among female patients, concomitant use of statins, fibrates or NSAIDs was associated with decreased likelihood of fatality, whereas concomitant alcohol use increased the risk of fatality. In men, concomitant use of statins was associated with decreased likelihood, whereas use of sympathetic stimulants or alcohol was associated with increased likelihood. Thus, this study supports the notion observed in numerous experimental studies that net tissue damage is determined by the balance between injury and repair.

Clinical course and natural history

In the vast majority of DILI patients who survive the initial liver injury, biochemical and histological recovery is complete, but a small proportion of patients may develop chronic liver disease (chronic DILI). In the first study investigating the natural history of DILI, a high proportion of patients with persistent abnormalities were found, but these patients were identified through a histological database, indicating a selection bias [22]. A prospective follow-up of DILI patients registered in the Spanish hepatotoxicity registry revealed a 5.7% incidence of chronic DILI [23]. Recently, 6 months after enrollment in the prospective DILIN study, 14% of patients had persistent laboratory abnormalities [3••].

However, whether these patients or other patients reported to have chronic DILI will experience liver-related morbidity or mortality is not clear. A recent follow-up study of DILI patients from Sweden with a mean follow-up of 10 years revealed that development of a clinically important liver disease after severe DILI (all had jaundice initially) was very rare [24•]. A total of 23 of 685 DILI patients who had survived acute DILI were hospitalized for liver disease during the study period and five had liver-related mortality [24•]. Among these patients, five out of eight did not have an identifiable cause of cirrhosis, in which DILI might have played a role for this development. A significantly longer duration of drug treatment before the diagnosis of DILI was significantly more common in patients who experienced liver-related morbidity and mortality than in those who did not.

All available data indicate that continuing medication after DILI onset is ominous. Thus, prompt recognition of DILI and cessation of therapy is not only important to decrease the risk for acute liver injury but may also avoid chronic consequences of DILI.

Brinker *et al*. [25•] reported the clinical characteristics of patients with suspected telithromycin-induced hepatotoxicity. Out of 42 patients retrieved, five had a severe outcome such as death or liver transplantation. Typical clinical features were very short latency (median 10 days) and abrupt onset of fever, abdominal pain, jaundice and sometimes ascites even in cases that resolved. The range of onset or signs of the liver injury was 2–43 days. Interestingly, among seven patients with latency of 3 days or less (n = 4 at 2 days; n =

3 at 3 days), only one patient reported previous exposure to telithromycin. Unusually short latency period after initiation of treatment with this drug, as brief as 1–2 days, makes this series very intriguing. Idiosyncratic DILI develops rarely so rapidly. However, other drugs with this 'signature' of remarkable short latency include fluoroquinolones that may also have 1–2 days of latency period [26].

The management of suspected idiosyncratic DILI includes exclusion of competing etiology, prompt cessation of the suspected agent(s) and appropriate supportive care. In rare instances of fulminant liver failure or severe cholestatic injury caused by DILI, orthotopic liver transplantation can be life-saving. The US Acute Liver Failure Study Group recently reported the result of their experience with intravenous *N*-acetylcysteine (NAC) to treat acute liver failure caused by causes other than acetaminophen. In this prospective, double-blind trial, patients with acute liver failure (nonacetaminophen) were randomized to receive NAC or placebo infusion for 72 h [27••]. Acute liver failure caused by DILI ($n = 45$) represented the single largest group among 173 patients who were randomized. Although the overall survival at 3 weeks was not significantly different between the groups, the transplant-free survival was significantly better among those patients randomized to NAC (40 vs. 27%, $P = 0.043$). The benefits of NAC were primarily seen in patients with early course of the disease with coma grade I–II (52 vs. 30% transplant-free survival) but not in those with advanced coma grade (III–IV) at randomization. When the overall and transplant-free survival of the four largest etiologic groups was considered, patients with DILI and hepatitis B virus (HBV) showed improved outcome in comparison with the AIH and indeterminate groups. In the DILI patients, transplant-free survival was 58% for those receiving NAC compared with 27% for those receiving placebo. Therefore, this study suggests that therapy with intravenous NAC should be considered in patients with acute liver failure due to idiosyncratic DILI.

Conclusion

Though rare, DILI must be considered in all patients with abnormal liver functions. Recent data highlight antibiotics, central nervous system agents, herbal/dietary supplements and immunomodulatory agents as the most common causes of DILI in the United States. Hepatocellular injury patterns are more common in younger patients and cholestatic patterns in older patients. An association between certain HLA genotypes and risk of flucloxacillin-related DILI has been established. The limitations of current instruments to measure causality in DILI may be minimized by the use of expert panel opinions, while efforts are underway to establish reliable biomarkers of DILI. Idiosyncratic DILI was shown to be dependent on both the daily dose and the extent of the hepatic metabolism of drug. Although chronic DILI may occur, the development of clinically important liver disease after severe DILI is rare. NAC seems to be beneficial for patients with acute liver failure caused by medications or herbal agents.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 290–291).

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