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DRUG-INDUCED LIVER INJURY (P HAYASHI, SECTION EDITOR)

Global Epidemiology of Drug-Induced Liver Injury (DILI)

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Abstract

Purpose of Review Drug-induced liver injury (DILI) is not an uncommon liver disease in many parts of the world. DILI is one of the most common causes of acute liver failure in most countries. The current review summarizes the global epidemiology of DILI.

Recent Findings The number need to harm in terms of DILI due to amoxicillin-clavulanate was approximately 1 out 2300, but was higher for azathioprine (1 out of 133) and infliximab (1 out of 148). A retrospective Chinese study showed the highest rate of DILI in hospitalized patients with an incidence of approximately 24 patients per 100,000 annually with a more favorable prognosis in the DILI cohort than previously reported from Europe, the USA, and Asia.

Summary Although large DILI registries from Europe and the USA have collected much data, more prospective studies with continual enrollment are needed particularly as new therapies such as immune modulatory and oncological medications with longer half-lives and latencies come to market.

Keywords DILI · Hepatotoxicity · Epidemiology · Incidence · Prognosis · Global

Introduction

Hepatotoxicity, drug-induced liver injury (DILI), and adverse liver reactions are terms used interchangeably. For most drugs, *idiosyncratic* hepatotoxicity is a rare adverse reaction. Apart from patients who participate in clinical trials who have their liver tests monitored regularly, it is very difficult to ascertain the true incidence of DILI. Most of the information on DILI comes from case-control studies or retrospective cohort studies [1–7]. Only a few prospective studies on DILI have been undertaken [8–12]. Current and ongoing studies are prospective recruitment of cases in the Spanish Hepatotoxicity Registry [8] and in the drug-induced liver injury network in the USA [10]. Few population-based studies have been performed. Two in Europe and one recently in the USA are notable [13, 14, 15•].

With growing registry and cohort data, some recurring themes are emerging. DILI from conventional and herbal and dietary supplements (HDS) is currently one of the most common causes of acute liver failure across the globe including Europe [4, 16], the USA [17–19], Japan [20], China [21], and India [22]. Indeed, HDS-induced liver injury in the eastern part of the world has been a major problem for a long time [6, 9, 12, 21], but such injury is on the rise in the west as well [23–25]. Anabolic steroids have been recognized for decades as a cause of liver injury [26••] but only recently have registries put forth studies with large number of patients that can fully illustrate important clinical and genetic characteristics of this unique liver injury [27, 28•].

Besides HDS and anabolics, other recent publications are providing valuable and clinically useful data for individual and classes of prescription medications. Perhaps most important are recent cohort studies that describe chemotherapy and immune-modulator hepatotoxicity including multiple sclerosis medications and anti-tumor necrosis factor (anti-TNF) agents [29–33]. A recent study has examined DILI by modern volatile anesthetics, an important but under studied group of agents [34]. In other words, growing epidemiologic data are filling in knowledge gaps for both overall DILI and DILI from specific agents. The pace of publications has accelerated since

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the 1990s particularly from Europe, North America, and Asia. These data are particularly useful for the clinician as they assess the probability of DILI in their patients.

Europe

Epidemiological research in Europe on drug-induced liver injury (DILI) took off in the early 1990s [2, 35]. These early-source populations were from large general practice or study drug databases [1, 2]. Limitations of these studies were the retrospective design, making accurate diagnosis of DILI difficult. All cohorts were selected according to their use of the study drugs. Searches were done for any liver disorder and case histories reviewed [1, 2]. In 2004, de Abajo et al. provided quantitative estimates on the absolute and relative risks of acute clinically apparent DILI [2]. The strongest associations for acute DILI were seen with chlorpromazine, azathioprine, and sulfasalazine at approximately 1 per 1000 users. Risk of approximately 1 per 5000 users was observed for the antiepileptics carbamazepine and valproic acid [2]. The occurrence of amoxicillin-clavulanate was found to be 1 per 10,000 users [2]. Diclofenac was the only NSAID drug associated with an excess risk but was relatively lower at 1 per 15,000 users [2]. The limitations of these studies were the retrospective design, exclusion of over the counter drugs, and HDS products [2]. The retrospective study design lends itself to exclusion of otherwise good cases because of lack of diagnostic evaluation and follow-up. Therefore, underestimation of DILI probably occurred. The crude incidence of DILI was found to be 2.4 cases per 100,000 inhabitants annually [2].

In a retrospective single-center study from Sweden, a remarkably similar incidence of 2.3/100,000 was reported [5]. Among 147 patients hospitalized in the UK with elevated liver biochemistries, 13 (8.8%) were felt to be DILI cases. These 13 constituted 0.7% of the 1964 admissions [35]. A study from Switzerland found DILI in 1.4% of hospitalized patients but the DILI was not included among the diagnoses or in the physician's discharge letter in a high proportion of patients, highlighting the need for specific methodology that detects DILI beyond just discharge diagnoses [36]. In a population survey recruitment, 126 adult patients with DILI were prospectively enrolled over a 9-year period, in 12 hospitals in Barcelona [37]. Drug consumption data were used to estimate the exposed population. Isoniazid, pyrazinamide, rifampicin, amoxicillin with clavulanic acid, erythromycin, chlorpromazine, nimesulide, and ticlopidine presented the highest DILI risk [37].

The first prospective population-based study came from France, and the incidence of DILI was estimated at 14 per 100,000 inhabitants per year [13]. All new cases of symptomatic DILIs were collected by general practitioners and gastroenterologists, in order to maximize the capture of cases and cover the spectrum of clinically relevant severity [13]. Among these cases of suspected DILI, 12% required hospitalization and 6% died.

A more recent population based study from the whole country of Iceland during a 2-year study period demonstrated a slightly higher incidence of 19 cases per 100,000 per year [14]. In a total of 96 patients (56% females), DILI was caused by a single prescription medication in 75% of the cases, by multiple agents in 9% and dietary supplements in 16%. The most commonly implicated drugs were amoxicillin-clavulanate (22%), diclofenac (6%), azathioprine (4%), infliximab (4%), and nitrofurantoin (4%). The median duration of therapy was 20 days, and 23% were hospitalized for a median of 5 days (range, 2–8) and one patient died as a result of the liver injury [14]. Similar to other cohort studies from Europe [2–5, 8, 38], antibiotics were the most common type of drugs leading to DILI [14]. Amoxicillin-clavulanate was the most common drug, occurring in 1 out 2350 users [6].

A recent hospital-based study from Germany was at odds with previous studies identifying drugs for neurologic disorders as the most commonly associated class associated with DILI [39]. This study stands in distinction from other European data that typically identifies antibiotics as most common. Another observational study among German inpatients suggested that selective serotonin reuptake inhibitors were less likely than older antidepressants to precipitate to DILI [40]. It is unclear how much of these differences in particular medications and classes between countries related to true differences in risk or differences in prescribing practices, need, and availability.

As for severe liver injury from medications, antibiotics and disulfiram standout in Europe. Over a 6-year study period, in tertiary referral center in Denmark, 6 patients underwent liver transplantation and another 9 patients died from *idiosyncratic* DILI, most often from disulfiram and antibiotics [41]. These etiologies were very similar to a Swedish study of DILI associated with a fatal outcome [4]. Furthermore, the results of the Danish study support and document the hepatotoxicity potential of disulfiram [42].

The USA

DILI is the most frequent cause of acute liver failure in the USA [17–19]. In a retrospective study of liver test abnormalities in the USA from the early 1990s, drug-associated liver enzyme abnormalities were the most common cause [43]. However, these results have not been reproduced. In a retrospective single-center study from Michigan. Here only 32 (0.8%) of 4039 patients referred for acute and chronic liver disease were found to have DILI [44]. Antibiotics, mostly amoxicillin/clavulanate, minocycline, nitrofurantoin, trimethoprim-sulfamethoxazole, were the class of drugs most

frequently implicated whereas amiodarone was the single agent most commonly associated with liver injury [44]. In another study from the USA, acute liver disease as a result of non-alcoholic etiologies was caused by DILI in 4% of cases with jaundice [45]. Most cases were due to acetaminophen whereas only 0.7% were considered to be due to other agents [45]. Overall 6% of patients were ineligible for analysis due to lack of data in the medical records potentially underestimating the number of patients with idiosyncratic DILI [45].

Some retrospective studies have been undertaken in the USA, based on search for ICD-9 codes [46, 47]. These studies revealed relatively low number of cases and are probably a large underestimation of the real incidence of DILI due to inaccurate or incomplete coding. Acute liver injury ICD-9-CM codes combined with a text search of the medical record yielded the greatest number of DILI cases but had lower specificity than other search methods [46].

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) established the Drug-Induced Liver Injury Network (DILIN) in 2004. The DILIN has collected and analyzed over 1000 cases of severe liver injury caused by prescription drugs, over-the-counter drugs, and herbal and dietary supplements (HDS). Although not population-based, the DILIN has gained and established considerable amount of knowledge and provides important information regarding relative prevalence of agents causing DILI [10, 11]. It is unique because the diagnosis is based on protocolized blood test and imaging evaluation, 6 months of follow-up and adjudication of DILI diagnosis by 3 DILIN hepatologists initially. Final diagnosis is based on 5-level scale of likelihood and is approved by the larger Causality Committee of all DILIN investigators.

The major agents associated identified in the DILIN have been quite similar as in European cohorts with antibiotics and antiepileptics being the largest classes of agents represented [3, 8, 14]. Most of the drugs implicated are old drugs that have been marketed for a long time [10, 11]. However, three drugs marketed during 2003–2007 (duloxetine, leflunomide, telithromycin) were identified to cause liver injury by 2008 [10]. Since the first case series published in 2008 [10], more than 60 papers have been published by the DILIN in both adults and children, many related to commonly prescribed medications describing clinical injury pattern, histology, and course [48–54]. A full listing of publications can be found at the DILIN website (www.dilin.org (accessed 5/4/2019)).

As in Iceland and Spain, HDS is an increasing cause of hepatotoxicity. The DILIN initially reported that 9% of their cases were HDS-related [10], but the percentage has risen to 20% over the last 10 years [23]. HDS DILI has also been shown to be more severe with a higher percentage being fatal or needing transplant [23]. Extract of green tea was the most prevalent hepatotoxic ingredient among HDS cases in the US DILIN (6/28, 21%) and Iceland (4/15, 27%) [14, 23].

The first population based study in the USA investigated the incidence of idiosyncratic DILI in the state of Delaware, which has a population of approximately 930,000 [15•]. During one year (2014), 20 individuals met the definition of DILI corresponding to an incidence rate of 2.7 cases per 100,000 adults, mean age 51 years, and 57% women [15•]. Overall, 36% were attributed to antibiotics, 21% to other drugs, and 43% to HDS, and in the total study cohort, 50% presented with jaundice. All recovered without the need for liver transplantation. The study found much lower incidence rates than population-based studies of DILI in Europe [13, 14] and is probably underestimating the true incidence. The study enrolled patients referred from gastroenterologists only and did not specifically target hospitalized patients.

Drug-induced liver failure was the focus of another US study that investigated the population-representative incidence of drug-induced acute liver failure (DIALF) in the Kaiser Permanente healthcare system serving over 3 million people in California [55]. Excluding acetaminophen, the most common cause, the incidence rate of *idiosyncratic* DIALF was just 0.59 per 1,000,000 person-years. However, of these, HDS were more commonly implicated than conventional drugs [55]. Similarly, in a study identifying patients with DILI from a histological database, the most common etiologies associated with DILI were supplements and herbal products (31%), followed by antimicrobials (14%), chemotherapeutics (11%), antilipidemics (7%), and immunomodulatory agents (7%) [56]. Therefore, DIALF is rare, but HDS is a leading cause compared with non-acetaminophen medications causing this severe injury.

Asia

One of the first studies on DILI from Asia was a small study from Singapore, which demonstrated that Chinese traditional medicines dominated the drugs implicated in DILI [9]. Other subsequent studies from Japan [57] Korea [12, 58], China [21, 59, 60••, 61, 62, 63], Taiwan [64], Thailand [62], and India [6, 22, 63, 65, 66] have also shown HDS to be the most common cause of DILI in these Asian countries. In a prospective nationwide study of DILI from Korea during a 2-year period in a number of referral university hospitals, the extrapolated incidence of hospitalization due to DILI was 12 per 100,000 persons per year [12]. Traditional and herbal medicines were the most common cause of DILI, being implicated in over 70% of cases [12]. The vast majority of injuries were hepatocellular (ALT and AST elevation predominant) as opposed to cholestatic (alkaline phosphatase predominant), similar to other studies on HDS liver injury [23, 24].

In both India and China, tuberculosis (TB) is a still a major health issue and it is therefore not surprising that liver injury from drugs against tuberculosis is commonly

observed in these countries [6, 22, 59, 60••, 61]. In a recent study by Devarbhavi et al. from Bangalore, India, approximately 72% of patients with drug-induced acute liver failure (DIALF) had been on combination of anti-TB drugs [22]. DIALF carried a high mortality as 66% ($n = 84$) of patients, including 13 children (62%) died and only 34% of the total cohort recovered spontaneously [22]. In a single center, Chinese study among hospitalized patients, Chinese herbal medicine (CHM) was identified as the primary cause of DILI at 36% of the patients. The overall mortality was 8.6% [59]. Model for End-Stage Liver Disease (MELD) score and albumin were shown to be independent predictors of outcome in patients with DILI [59]. Another study from Beijing, China, CHM was implicated in 563 cases (28%); 870 cases (44%) were caused by western medicines (WM) and the remaining patients (28%) by the combination of WM and CHM. Compared with WM, CHM-induced liver injury was more often observed in females (51% vs. 71%, $P < 0.001$), more frequently had positive rechallenge (8.9% vs. 6.1%, $P = 0.046$), hepatocellular injury (89% vs. 62%, $P < 0.001$), and a higher mortality (4.8% vs. 2.8%, $P = 0.042$).

Data on the incidence and etiology of DILI patients in mainland China has recently been published from a retrospective study [60]. Data was collected on "suspected" DILI cases based on hospital discharge diagnosis. Cases were "confirmed" using the Roussel Uclaf Causality Assessment Method (RUCAM) of DILI diagnosis with equivocal cases being reviewed in detail. All patients were hospitalized from 2012 through 2014 at 308 medical centers in mainland China [60]. Discharge diagnoses lack proven accuracy, and the RUCAM has never been validated in HDS or CHM cases in particular, so the claim of 25,927 confirmed cases is problematic. Those caveats aside, the results are interesting and intriguing. As in other studies from Asia, hepatocellular type of liver injury dominated perhaps due to the high proportion of CHM injuries (27%), followed by anti-TB drugs (22%) [60]. Chronic DILI was reported to be relatively frequent (13%) but few received a liver transplantation ($n = 2$) and only 102 patients died (0.39%) (66). The annual incidence was estimated to be 23.8 per 100,000 inhabitants, which is higher than the incidence in North American (2.7 per 100,000) [15•], French (13.9 per 100,000) [13], and the Icelandic (19.1 per 100,000), all three of which were prospective and population-based [14]. Although the authors have collected the largest DILI cohort published so far, the study is an outlier in terms of prognosis in all other DILI studies and in terms of the frequency of DILI being higher in a retrospective cohort than other studies.

Conclusions

Publications on DILI epidemiology began to accelerate in the early 1990s, starting with data on drug consumption and liver-related diagnoses obtained from the general practice research database in the UK. Since then, a handful of themes and studies are worthy of mention in summary. The first prospective population-based study on DILI came from France in the late 1990s and found an incidence of 13.9 patients per 100,000 annually. The Spanish Hepatotoxicity Registry started in 1994, which consisted of a cooperative network of clinicians and researchers interested in DILI, published their first 10 years of experience in 2005. Since then, it has remained an ambitious effort and mainstay in the field of DILI, producing several landmark studies. In 2004, the NIH-funded DILIN started a similar prospective study on DILI patients in selected tertiary referral centers in the USA. It has joined the ranks of the Spanish Registry as a significant contributor to our knowledge of DILI epidemiology with more than 60 papers. In the west, non-TB antibiotics and NSAIDs seem to predominate with HDS and immune modulators on the rise. Very recently, data from Asia, mostly China and India, have emerged. The most important information from Asia thus far has been the preponderance of liver injury due to herbal and dietary supplements, traditional (homeopathic) medicines, and allopathic medications for TB.

Our understanding of the epidemiology of DILI across the globe has come a long way since the 1990s, and it will become even clearer in the years to come. However, the field will always face the challenge of changing demographics, emigration, immigration, and changes in disease states and agents applied. Keeping abreast of these data will be paramount for the clinician and researcher alike.

Compliance with Ethical Standards

Conflict of Interest Einar S. Björnsson declares no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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- •• Of major importance

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