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EDITORIAL

"Drug-Induced Liver Injury Clinical Consortia: a global research response for a worldwide health challenge"

1. Introduction

The hepatic safety of drugs is a major concern of the pharmaceutical industry throughout the whole process of drug development. Whereas the intrinsic toxicity of a few drugs will become evident during the early stages of this process (i.e. in cellular cultures or animal studies), for the bulk of hazardous medications, which will injure the liver in rare occasions, the hepatotoxicity profile may remain hidden in both preclinical and clinical phases. Actually, clinical trials are able to identify relatively common adverse reactions (i.e. occurring at a rate greater than 1 per 1000 exposed subjects), but are generally underpowered to detect the low incidence of idiosyncratic drug-induced liver injury (DILI).[1] The multifactorial nature of the idiosyncratic chemical damage targeting the liver depends on the interaction of the drug physicochemical properties with the host factors that make the subjects susceptible on rare instances.[2] No reliable methods for accurately predicting the occurrence of toxic liver damage on a given individual are still available. Hence, information on the true hepatic safety profile for the bulk of drugs relies on observational studies and requires the exposure of hundreds of thousands of subjects once the medication reaches the market. If an 'outbreak' of reports of liver damage linked to a particular drug use were detected, regulatory measures, including warnings and withdrawals, to limit the number of affected individuals would follow. Nowadays, however, many old drugs with hepatotoxic potential still remain in therapeutic use either because their true risk figures have not been fully recognized or due to a favorable benefit/risk balance (i.e. flucloxacillin, amoxicillin-clavulanate).

Until recently, hepatotoxicity had not received enough attention from the academic investigators due to its relative rarity and data on hepatotoxicity of drugs were mostly compiled by the pharmaceutical industry under restrictive access rules or were simply unavailable. Indeed, the absence of valid diagnostic biomarkers means that DILI remains a 'diagnosis of exclusion', which limits the 'scientific' accuracy of the information retrieved and may discourage investigators from being involved on this topic. All these limitations represent an important barrier for proper case identification and characterization as well as for the availability of consistent epidemiological data.

2. Epidemiology of DILI

The epidemiology of DILI has been explored using different approaches yet traditionally has been a matter of the pharmacoepidemiology rather than of the field of clinical hepatology. Several population-based case–control studies have took advantage of the general practice research database in the UK, which enables associate prescription data to clinically meaningful events such as death, hospital admission and diagnosis at discharge. This database was used to estimate in a large population (>5 million person-years and 5000 controls subjects) from 1994 to 1999 the crude incidence of DILI that was found to be 2.4 per 100,000 persons per year.[3] All patients referred to a consultant or hospitalized for a liver-related diagnosis were identified, and records reviewed manually. The list of drugs was topped by well-known 'hepatotoxic' compounds such as chlorpromazine, amoxicillin-clavulanic acid, flucloxacillin, macrolides and tetracyclines, among others, but also included apparently 'innocent' bystanders, such as metoclopramide, chlorpheniramine and betahistine.[4] This study illustrates the limitations of retrospective designs based on prescription data regarding the adjudication process, one of which is that alternative causes of liver damage cannot be thoroughly excluded and the other being that over-the-counter/herbal agents are not taken into account.[3] Unsurprisingly, the incidence obtained in this analysis was lower than that of prospective designs.[5,6] Other retrospective study cohorts used the Kaiser Permanent Northern California database as a surrogate of a wide population sample to determine the incidence of serious DILI leading to acute liver failure and death.[7] An important limitation of this approach is that to define liver events these studies used ICD-9 (international classification of diseases) codes, which have poor accuracy, leading to low

specificity and sensitivity for DILI recognition. Up to date, there are very few true population-based prospective studies aimed to determine the incidence of DILI. A pioneer study prospectively monitored 81,000 inhabitants of an isolate region of northern France, considered ideal for capturing every potential DILI incident.[5] Of the 95 cases retrieved, only 34 were considered possible, probable or definite DILI, yielding an overall incidence of 14 cases per 100,000 inhabitants per year. The most common implicated medications were antibiotics (25%), psychotropics (22%) and hypolipidemics (12%). During follow-up, three (10%) of the DILI patients died of liver disease. A recent population-based study took advantage of the excellent and centralized medical care system enjoyed by the well-characterized population of Iceland (about 250,000 adults).[6] Over a 2-year period, 96 patients qualified for DILI (56% female), demonstrating an incidence of 19 cases per 100,000 per year. DILI was caused by a single prescription medication in 75% of the cases, dietary supplements in 16% and multiple agents in 9%. This study is unique because for the first time both an accurate denominator (the exposed population) and the incidence of DILI for specific drugs could be calculated. Indeed, the Iceland study arguably provides the better incidence data because it encompassed the entire population of a nation with robust records of prescriptions written and DILI events. Antibiotics ranked first again among the list of culprit drugs, the estimated risk of liver injury for amoxicillin/clavulanate being 1 per 2350 users, an incidence higher than previously reported.[3] Interestingly, however, the figures of jaundice (27% of the patients) and hospitalization (23%) suggest that the majority of cases were asymptomatic. Indeed, the criterion for cases to qualify (alanin-aminotranferase > 3 × upper limit of normal) could enable the inclusion of some cases that would 'adapt' even with continuation of the drug, thus not representing true DILI.[8] Although population-based studies are an invaluable approach to estimate DILI incidence, considering the impact that genetic susceptibility has on idiosyncratic DILI, it is hard to extrapolate the estimated risk linked to specific drugs from people with a specific genetic ancestry to populations with different genetic backgrounds. Most importantly, they require substantial resources that limit their generalized use and maintenance over time.

3. Clinical DILI consortia

Some of the above-mentioned limitations have been overcome by the development of DILI Registries across the world.[9–11] In 1994, the first formally prospective DILI Registry was set-up in Spain.[9] At this time, it was already evident that progress in the understanding of idiosyncratic hepatotoxicity with regard to causative agents, clinical presentation, risk factors and outcome was precluded by the lack of a number enough of well-vetted cases. Hence, a cooperative multicenter approach was set-up and maintained throughout the years. The network is open to the affiliation of all hospital units interested in the project. A structured protocol was agreed on and used to gather detailed information on patients' demographics, pharmacological history, clinical, laboratory and histological features. Patients in the Spanish DILI Registry [12] are followed until death/liver transplantation or full recovery. Biological samples from well-phenotyped patients also enable a repository for genetic and mechanistic studies including testing of current and future biomarkers. In 2011, a new branch of the Spanish DILI Registry, the SpanishLatin DILI Registry, was established in Latin America.[10,13] In addition, The National Institutes of Health patronized the Drug-Induced Liver Injury Network that was launched in 2003 in the US, and its results are periodically updated.[11,14] Prospective DILI consortia make careful case adjudication using expert opinion clinical judgment along complementary standard causality assessment by the Roussel Uclaf Assessment Method .[9–11]

A consistent characteristic of DILI Registries is the inclusion of patients sicker than those identified in epidemiological efforts,[5,6] with around 70% of the patients jaundiced at presentation and half of them requiring hospitalization (Table 1),[9–11] so the proportion of non-'true' DILI cases is probably negligible. This

Table 1. Demographics and clinical data of DILI patients included in the different prospective Registries.

	Spanish DILI Registry [10]	SLATIN DILI Network [10]	Iceland [6]	DILIN [11]
DILI cases, N	867	200	96	899
Age year, mean	54	51	55	49
Female sex, %	49	59	56	59
Jaundice, %	68	67	27	70
Hospitalization, %	59	46	23	55
Type of injury, %				
Hepatocellular	64	54	42	54
Cholestatic	19	27	32	23
Mixed	17	19	26	23
Liver related death or transplantation, n (%)	4	5	1	6.6

selection bias, probably related to the fact that DILI patients are mainly identified in hospital units, nevertheless, strengthens the phenotypic and genotypic data collection. Interestingly, the phenotypes of liver damage as characterized by liver biochemistry (hepatocellular, cholestatic and mixed) overlap among registries as does the severity.[9–11] New clinical findings provided by statistical analysis of the large DILI cohorts from the consortia include the recognition of female sex, hepatocellular type of damage and high bilirubin levels as risk factors for fulminant liver failure and death, [9,15] the influence of age and sex on the phenotypic expression of hepatotoxicity [16] and the higher mortality risk in patients with preexisting liver disease.[11] DILI Registries have also provided consistent figures on the therapeutic group of drugs most commonly implicated (Table 2) [9–11] and the growing problem with herbals and dietary supplements in the US.[11] A well-characterized and large cohort of DILI cases is required to explore genetic susceptibility. DILI Registries have enabled to carry out genome-wide association studies in patients with hepatotoxicity induced by specific drugs, which revealed strong human leukocyte antigen (HLA) associations, including *HLA-B*5701* (flucloxacillin) and HLA class II *DRB1*1501-DRB5*0101-DQB1*0602* haplotype (amoxicillin-clavulanate).[17] Although the positive predictive value of these associations is low precluding its use in pretherapy screening, its high negative predictive value could be of help for diagnostic purposes.[18] These findings are a significant addition in the field of hepatotoxicity and have changed the conceptual view on DILI pathogenesis, underscoring the fundamental role of the adaptive immune system.[8,17] In the near future, other 'omics' will be tested and further advances in pathogenesis, diagnosis and prognosis are expected, a reason enough to support the existing registries and to promote new ones.[19]

4. Expert opinion

DILI is a global health problem concerning transversally to a broad audience of clinical practitioners from several medical and surgical specialties, clinical and basic investigators, as well as people from regulatory affairs and pharmaceutical companies. DILI is a challenging form of liver disease that is capable of mimicking virtually any other liver disorder being a diagnosis of exclusion as no specific biomarkers are still in place, which represents a major impediment for advancing in correct phenotyping and genotyping of affected subjects. The necessity of concerted efforts to obtain reliable information on DILI causal agents, phenotypes and risk factors stimulated groups in Europe and the US to develop large DILI prospective registries in the last two decades. In other parts of the world such as China, India and South Korea, similar efforts are ongoing. A pan-national initiative in Europe, the EuroProDILI Registry, fostered by the European Association for the Study of the Liver, is aimed at prospectively collecting serial biological samples from DILI onset until recovery for exploratory mechanistic biomarkers studies. Besides, this multinational network would enable us to perform clinical trials during the very acute phase of hepatotoxicity. In addition, the International Drug Induced Liver Injury Consortia –that comprise numerous academic centers across the world with financial support from pharmaceutical companies – has enabled us to carry out genome-wide association studies in well-phenotyped DILI patients, identifying important signals related to the HLA locus in chromosome 6. In the last few years, Europe has supported programs for the development of

Table 2. Therapeutic group of drugs implicated in DILI across the prospective Registries.

DILI Consortia (reference)	Spanish DILI [10]	SLATIN DILI [10]	Iceland [6]	DILIN [11]
Years	1994–2015	2012–2015	2010–2011	2004–2013
Type of Registry	National (43 centers)	Multinational (10 countries)	Population-based study	National (5 centers)
DILI cases	906[a]	200	96	899
Most frequent drug classes, n (%)	Antiinfectives 333 (37)	Antiinfectives 48 (24)	Antibiotics 36 (37)	Antimicrobials 408 (45)
	Nervous system 131 (14)	Musculo-skeletal system 36 (18)	Dietary supplements 15 (16)	HDS 145 (16)
	Cardiovascular system 98 (11)	HDS 19 (10)	Inmunosuppresant drugs 10 (10)	Cardiovascular drugs 88 (10)
	Musculo-skeletal system 97 (11)	Genito urinary system and sex hormones 18 (9)	Psychotropic 7 (7)	Central nervous system agents 82 (9)
	Anti-neoplastic drugs 69 (8)	Nervous system 18 (9)	NSAIDs 6 (6)	Anti-neoplastic drugs 49 (5)
HDS, n (%)	51 (6)	19 (10)	15 (16)	145 (16)

[a]The actual number of patients was 867 but in 39 patients there were 2 DILI incidents.
Antiinfectives refers to antibiotics, antituberculosis drugs, antifungals and antivirals.
HDS: herbals and dietary supplements.

prediction tools of drugs' potential for hepatotoxicity during the early preclinical stages of drug development (MIP-DILI project) and biomarkers for prediction, detection and monitoring of DILI (the Safer and Faster Evidence-Based Translation). In parallel, the development of quantitative system toxicology approaches to improve the understanding of the liver safety of new medicines will benefit from the existing databases. In the near future, efforts must also be directed to further agree on terminology and causality assessment criteria among DILI investigators across the world looking for integration and comparability on the generated data to move toward safety personalized medicine. All these objectives are attainable and are worth to be pursued.

Declaration of Interest

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