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MINIREVIEWS

Drug-induced liver injury: Towards early prediction and risk stratification

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Abstract

Drug-induced liver injury (DILI) is a hot topic for clinicians, academia, drug companies and regulators, as shown by the steadily increasing number of publications and agents listed as causing liver damage (http://livertox.nih.gov/). As it was the case in the past decade with drug-induced QT prolongation/arrhythmia, there is an urgent unmet clinical need to develop tools for risk assessment and stratification in clinical practice and, in parallel, to improve prediction of pre-clinical models to support regulatory steps and facilitate early detection of liver-specific adverse drug events. Although drug discontinuation and therapy reconciliation still remain the mainstay in patient management to minimize occurrence of DILI, especially acute liver failure events, different multidisciplinary attempts have been proposed in 2016 to predict and assess drug-related risk in individual patients; these promising, albeit preliminary, results strongly support the need to pursue this innovative pathway.

Key words: Hepatotoxicity; Predictivity; Risk assessment; Safety

Core tip: The interest in drug-induced liver injury (DILI) is growing, especially in 2015-2016, with pioneering studies addressing DILI annotation, *i.e.*, risk stratification of drugs capable of causing liver damage. The latest experiences from worldwide consortia provided promising data, although there is still room for improvement before reaching an algorithm capable of discriminating hepatotoxic from non-hepatotoxic compounds, or at least of classifying high, intermediate and low risk drugs within the same therapeutic class. We should take advantage of integration of real-world data (*i.e.*, registries, healthcare databases, spontaneous reporting systems, literature) with cheminformatics to provide a comprehensive DILI risk score.

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INTRODUCTION

The year 2015 witnessed an outstanding scientific production of studies dealing with drug-induced liver injury (DILI) and the list of drugs capable of causing liver dysfunction needs constant update, thus making DILI an emerging safety issue requiring attention by academia, regulators, drug companies and clinicians, both in specialty and general practice[1,2].

A search in MEDLINE using the strategy "DILI or drug-induced liver injury or drug-induced liver damage or herb-induced liver injury or herb-induced liver damage or hepatotoxicity" yielded 2196 publications in 2015 (performed on June 7th, 2016) (Figure 1), with more than 2000 studies per year published in the past 4 years. The proportion among the different types of studies has not substantially changed over time, with pre-clinical investigations representing the majority of publications (more than 60% of total studies in 2015). This body of evidence has generated concern within the scientific community, especially among clinicians, who are not fully aware that a number of drugs are likely to affect liver function and must be therefore considered among the differential diagnoses in patients presenting with elevated transaminases.

DILI has tremendous impact on medical prescribing attitudes: The latest data confirmed that hepatotoxicity was the most commonly reported adverse drug reaction leading to drug withdrawal worldwide (81 cases; 18%)[3]. Several global registries (in United States, Latin America, Europe and China) have continued to update case series and implement completeness and accuracy of data[4]. It is interesting to note that antinfectives/antimicrobials are the most frequently implicated drugs in DILI reports across all data registries and population-based studies, with herbal and dietary supplements being an emerging concern especially in United States[5-7].

While population-based studies are useful to estimate DILI incidence (despite suffering the inability to account for genetic backgrounds), prospective registries across various DILI consortia allow careful case adjudication. It is worth mentioning that registries consistently enrolled sicker patients as compared to epidemiological studies, with 70% of the patients jaundiced at presentation and half of them requiring hospitalization, thus the proportion of non-"true" DILI cases is probably negligible. This selection bias, probably related to the fact that DILI patients are mainly recruited in hospital units, is useful to appreciate phenotypes of liver damage (hepatocellular, cholestatic and mixed) and investigate specific features or drug signatures: Female sex, hepatocellular type of damage and high bilirubin levels emerged as risk factors for fulminant liver failure and death[8], with higher mortality risk in patients with preexisting liver disease[9].

In this minireview, we highlight advances in DILI research, focusing on recent studies that, in our opinion, provide key contribution towards an unmet clinical need: Risk stratification of drugs capable of causing liver damage, also known as DILI annotation.

SUSPECTING AND DIAGNOSING DILI: A CURRENT DILEMMA

The contribution of drugs in DILI occurrence

Different drugs have been convincingly documented to cause liver injury in numerous case reports and case series[10]. Paracetamol has been consistently reported as a leading cause of acute liver failure, whereas chlorpromazine, halothane, sulpiride and amoxicillin-clavulanate such as found to be the most common drugs leading to hepatotoxicity in all prospective studies[11]. Apart from antibiotics, the list of top 10 drugs implicated in DILI cases (in terms of frequency) comprises statins (only rarely severe liver injury was likely to be associated with statins), antitumor necrosis factor antagonists (with infliximab being the most common implicated agent, with autoimmune features), and herbal and dietary supplements (with weight loss and bodybuilding products being the most frequent causes of serious hepatotoxicity)[12].

A risk of DILI greater than 100 per 100000 users was found for chlorpromazine and sulpiride. Drugs with an intermediate risk were amoxicillin-clavulanic acid and emerged with a risk of 10 per 100000 users[13]. All other drugs were found to be less than 10 per 100000 users.

Unfortunately, in most of the cases, DILI is unpredictable because of its idiosyncratic nature; in fact, only rarely have the precise underlying mechanisms been identified (*e.g.,* mitochondrial injury, reactive metabolites, biliary transport inhibition, and immune responses). Paracetamol is a well-known example of drug causing dose-dependent DILI.

Obtaining evidence-based data to support DILI diagnosis

DILI is a diagnosis of exclusion, thus strengthening the importance of anamnesis and clinical experience. Apart from ruling out competing causes (*e.g.,* viral infections), it is crucial in the clinician's mind to have information on the notoriety, *i.e.,* whether the drug is known or has the potential to cause hepatotoxicity. However, these evidence-based data are not always easily accessible[11].

The first aid is represented by the product information or summary of the product characteristics (in United States and Europe, respectively), which however is variable in terms of details and may also substantially differ in the labeling of liver risk[14]. The key information to be checked is the existence of contraindications in patients with pre-existing liver diseases and the presence of specific warnings on the risk of liver damage, with relevant precautions in appropriate monitoring and management. It must also be kept in mind that the wording of these documents follows rules that are not always patient- and physician-friendly. Other sources of information are therefore highly needed.

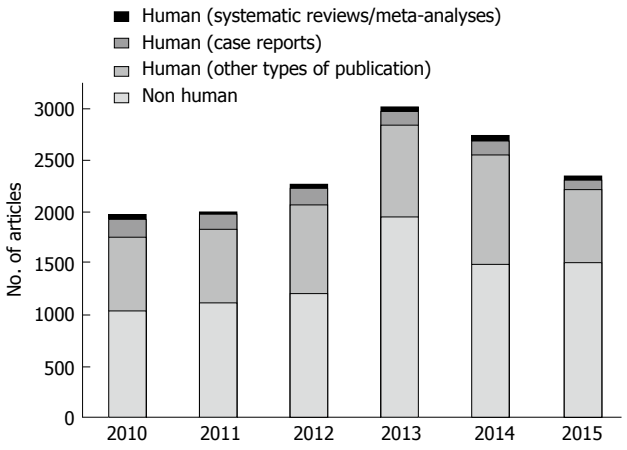

Figure 1 Trend in publication of articles on drug-induced liver injury, classified in terms of types of evidence. The search was performed in MEDLINE on June 7th, 2016, through automatic filters and keywords.

Ascertainment of the literature is the second step, which is a more challenging and time-consuming task. While some drugs have been convincingly documented to cause liver injury and clinical signatures have been demonstrated (*e.g.,* isoniazid, amoxicillin-clavulanic acid), for some agents only a few case reports are available and, most importantly, only in a minority critical clinical data are provided to ascertain the causative role of drugs[15].

The third source of data is represented by LiverTox® (http://livertox.nih.gov/), a public website set up to provide up-to-date, accurate, and easily accessible information on the diagnosis, causes, frequency and patterns of liver injury attributable to both prescription and nonprescription medications. Although LiverTox® is based on a thorough literature analysis, the quality of the published reports and the causality of the suspected liver injury reported are not provided.

Specific algorithms, such as the Roussel Uclaf Causality Assessment Method scale, have been proposed and validated to assess causality, although it should be recognized that these scores are particularly useful for regulatory and research purposes, *i.e.,* to verify a posteriori the likelihood of the association rather than to support a prospective diagnosis[16]. During the preapproval development process, Hy's Law (*i.e.,* ALT/AST > 3 ULN in combination with total bilirubin > 2 ULN in the absence of cholestatic injury - alkaline phosphatase < 2 ULN) is an essential part of the stopping rules to prevent hepatotoxicity, although it was never specifically validated in a clinical trial. Different research group have recently attempted to optimize the definition of Hy's Law and develop models for predicting acute liver failure in DILI, in combination with other biomarkers such as total bilirubin and platelet count[8,17]. However, whether such revised definitions can become part of clinical practice is yet to be determined.

Risk stratification of DILI in clinical practice: A dream or a reality?

Current expectations regard the development and implementation of risk stratification tools to assign a certain liver risk to a given drug. In other words, clinical research is trying to establish the so-called DILI annotation, a global score reflecting the frequency, causal role and severity of DILI for each drug[18]. This scenario recalls what occurred in the past decade with drug-induced QT prolongation and Torsade de Pointes (DITdP), which has been a largely debated regulatory issue for the past 20 years with still suboptimal tools for risk stratification in clinical practice[19]. With this experience in mind, we should immediately understand the importance of coordinating and harmonizing the various ongoing projects and the need to set up a global response to efficiently assess drug-related hazards. A parallel between DILI and DITdP is presented in Table 1.

Identification of baseline risk is the first step towards final risk stratification. DILI has a multifactorial nature with both environment- drug- and patient-related risk factors that may coexist and increase the likelihood of DILI occurrence.

Apart from age and sex, genetics plays a role, at least for some drugs. A recent genome-wide association study involving 620 European cases of DILI and 10588 population controls, the DRB1*16:01-DQB1*05:02 haplotype was identified as a risk factor for flupirtine-induced liver damage[20]. Although the inclusion of genetic tests in causality assessment may improve consistency and precision of DILI diagnosis as well as appropriateness of drug administration, there is only initial positive experience in clinical application of N-acetyltransferase 2 genotyping to determine the appropriate dose of isoniazid[21].

A current area of research deals with the identification of biomarkers, keeping in mind the aim of detecting patient's susceptibility to DILI prior to and during drug exposure, predicting the course of DILI once it occurs and differentiate DILI from other causes of liver injury. Among others, miR-122 expression was demonstrated to be a liver specific biomarker of paracetamol hepatotoxicity; high levels of High Mobility Group Box-1 with circulating colony stimulating factor-1 were correlated to poor prognosis and outcome in patients with established acute liver injury following paracetamol overdose; likewise, the prognostic utility of Keratin-18 has been proposed; notably, up-regulation of Kidney Injury Molecule-1, a marker of renal proximal tubular epithelia, could be a determinant of mortality in patients with paracetamol overdose and secondary kidney damage; finally, Glutamate Dehydrogenase might indicate hepatocellular necrosis, although lacking specificity in discriminating benign transaminases elevation from severe DILI occurrence. All these biomarkers, however, still require formal qualification before being considered for routine clinical use[22].

Among drug-related features, oral medications with high lipophilicity (*i.e.,* logP $\geqslant$ 3) administered at daily doses of $\geqslant$ 100 mg (known as the concept of the "Rule-of-2") have been associated with higher risk of DILI[23]. Bile salt export pump and multidrug resistance-associated protein 4 inhibitions have been also identified

Table 1 Similarities and differences between drug-induced torsade de pointes and drug-induced liver injury

	DITdP	DILI
Endpoint/biomarker	Surrogate, but well defined biomarker of risk (QT prolongation with specific thresholds)	Surrogate, but well defined biomarker of risk (transaminase elevation with specific thresholds)
Key mechanism	Largely described (dose-dependent hERG K^+ channel inhibition)	Only partially understood (different hypotheses)
Dose-response relationship	Dose dependent (with only a few exceptions)	Idiosyncratic, although dose-dependence exists
Regulatory impact	Pre-clinical and clinical guidelines (pre-marketing)	Clinical guideline (pre-marketing)
Clinical impact	Significant (a leading cause of drug withdrawal worldwide)	Significant (a leading cause of drug withdrawal worldwide)
Predictivity of pre-clinical assays	Reasonably good (new models under investigation)	Sub-optimal (especially for *in vivo* models)
Predictivity of clinical studies	Good (thorough QT study), albeit imperfect	Good (Hy's law), albeit imperfect
Role of genetics	Important (long QT syndrome)	Partially defined (only for some drugs)
Awareness (clinicians, regulators, drug developers, researchers)	Significant at all levels	Significant at some levels (drug developers, researchers)
Risk assessment tools (clinical)	Drug- and patient-related risk factors are well recognized (www.crediblemeds.org); CDSSs are under implementation	Drug- and patient-related risk factors are only partially recognized (www.livertox.nih.gov)
Causality assessment tools (clinical)	Not present, but the majority of TdP cases are drug induced (the so-called designated medical event); phenotype standardized	Specific, but challenging (several differential diagnoses)
Therapy	Magnesium sulphate, electrical cardioversion or isoproterenol (isoprenaline) or transvenous pacing (refractory TdP cases); removal or correction of precipitants, including drugs	No specific treatment other than drug discontinuation; liver transplantation may be required in acute liver failure cases

For details on DITdP[50-53]. CDSSs: Clinical decision support systems; DILI: Drug-induced liver injury; DITdP: Drug-induced torsade de pointes.

as important determinants of cholestatic DILI risk in humans[24,25]. However, the contents and the extent of information of these transporters in the summaries of the product characteristics may vary considerably between United States and Europe, especially for novel drugs[26].

Therefore, the recent literature attempted to annotate DILI risk through different approaches, all of which rely on the assessment of already available data. Among the various experiences, risk categories were created based on the information extracted from drug compendium, such as Physicians Desk Reference, and case reports (alone or integrated with literature and drug labeling)[18,27-32]. However, the validity of these published annotations is still a matter of debate because all methods present limitations and a gold standard to define DILI risk is lacking[33]. This is an unresolved concern, common to all drug-related safety issues.

Very recently, two different approaches stimulate interest in annotating DILI risk. Chen *et al*[34] combined the rule-of-two with the capacity to produce reactive metabolites and implemented a model to assess the risk of DILI onset and severity. Both dose-based and Cmax based-scores were calculated. Initial validation of this score indicated that half (19/38) of DILI cases with a dose-based DILI score $\geqslant$ 7 were associated with severe clinical outcome (*e.g.,* hepatic failure or death), while none of the cases with a DILI score < 3 were linked to severe liver injury. Statistical analysis revealed that a DILI score $\geqslant$ 7 and < 3 was significantly associated with higher or lower risk for severe hepatic outcome.

Conversely, Björnsson *et al*[35] classified drugs listed in LiverTox® website. Specifically, drugs were categorized based on the number of case reports (Category A $\geqslant$ 50 published reports, B = 12-50, C = 4-12, and D = 1-3) and another category, T, was added for agents leading to hepatotoxicity mainly in higher-than-therapeutic doses. In this study, fewer drugs than expected emerged with a documented hepatotoxicity. Among 671 drugs available for analysis, 353 (53%) had published convincing case reports of hepatotoxicity. Thus, overall, 47% of the drugs listed in LiverTox actually do not have evidence of hepatotoxicity. However, the main limitation of this analysis is that new drugs approved within the last five years were not included. Therefore, old drugs with consolidated clinical use are likely to result in higher risk. In fact, drugs in categories A and B were more likely than those in C and D to have been marketed for a long time, and both were more likely to have at least one fatal case of liver injury and reported cases of positive rechallenge. While there is little doubt that the majority drugs in category A and B are hepatotoxic, it is still unclear whether agents listed in C and D are really liver offenders.

A CRITICAL ANALYSIS OF THE DILI RISK SCORE: THE CASE OF DIRECT-ACTING ORAL ANTICOAGULANTS

Liver safety of direct-acting oral anticoagulants (DOACs) was highly debated in 2014-2015, when several publications highlighted possible occurrence of liver damage (including acute liver failure) during DOAC administration[36-39]. The majority of data are derived from case reports/series, which emphasized the relatively rapid time-to-onset and the concomitant reporting of drug that are implicated in liver damage or have the potential to result in drug interactions[39]. In particular, the time-to-onset from published case reports suggests

Table 2 Chemical and pharmacological properties of direct-acting anticoagulants likely to be associated with drug-induced liver injury risk in humans

	Dabigatran etexilate	Rivaroxaban	Apixaban	Edoxaban
Max daily dose (indication)[1]	220 (DVT prophylaxis) - 300 (NVAF)	5 (post ACS[2]) - 10 (DVT prophylaxis) - 20 (NVAF) - 30 (treatment of DVT/PE)	5 (DVT prophylaxis) - 20 (acute treatment of DVT/PE)	60 (NVAF and DVT)
Bioavailability[1]	6.50%	80%-100%	50%	62%
Protein binding	35%	> 90%	87%	55%
Cmax (ng/mL)	697 (at steady state after 400 mg/3 die)[54]	450 (multiple dose 30 mg/die)[55]	469 (single 20 mg dose)[56]	424 (90 mg daily at day 10)[57]
Lipophilicity (LogP)[5]	5.17	1.74	2.22	1.61
Biotransformation[1]	Conjugation forming 4 pharmacologically active acylglucuronides	Oxidative degradation of the morpholinone moiety and hydrolysis of the amide bonds	O-demethylation and hydroxylation at the 3-oxopiperidinyl moiety	Hydrolysis (mediated by carboxylesterase 1), conjugation or oxidation by CYP3A4/5 (< 10%)
Hepatic metabolism[1]	Only the prodrug is a substrate of P-gp; no induction/inhibition of principal isoenzymes of cytochrome P450	CYP3A4, CYP2J2 and CYP-independent mechanisms. Substrate of P-gp and BCRP	CYP3A4/5. Substrate of P-gp and BCRP	Substrate of P-gp
Structural alerts associated with RM formation	NO (aniline motif)[58,59]	NO (chlorothiophene and bis-anilide motifs)[42,58]	NO (para-methoxyaniline and bis-anilide motifs)[41,58]	ND (no published data in the literature)
Dose-based DILI Risk Score[3]	2.68	1.29	1.29	1.45[4]
Cmax-based DILI Risk Score[3]	2.98	1.87	2.02	1.82[4]

[1]From official European Summary of Product Characteristics; [2]Only in EU; [3]Calculated based on formulas reported by Chen *et al*[34]; [4]Calculated based on formulas reported by Chen *et al*[34] and assuming no RM formation; [5]Data obtained from Drug Bank (www.drugbank.ca; source: ALOGPS). ACS: Acute coronary syndrome; BCRP: Breast cancer resistance protein; DVT: Deep vein thrombosis; NVAF: Non valvular atrial fibrillation; ND: Not determined; RM: Reactive metabolites; DITdP: Drug-induced torsade de pointes.

that early evaluation of hepatic enzymes (*i.e.*, within the first month) may be considered at least in patients under complex treatment regimen with comorbidities; subsequently, liver function can be monitored on a yearly basis[40]. This is especially the case of rivaroxaban, for which a probable but unquantified association is likely to exist. Notably, rivaroxaban is the only DOAC reported in the list provided by Björnsson *et al*[35] and classified in category B.

Therefore, we applied the score developed by Chen *et al*[34] to DOACs and found intriguing data (Table 2). Based on these results, different issues emerge: (1) no DOAC appears to be associated with risk of severe liver damage (they all received a score well below the threshold of 7); (2) the highest score emerged for dabigatran; (3) the risk does not appear to be strongly influenced by dose or Cmax (there is only a small increase in Cmax-based score), or chemical motifs; (4) DOACs pose a lower risk as compared to warfarin (the dose-based risk score is 4.67, according to Chen *et al*[34]).

However, among DOACs, it is difficult to discriminate the agent with the highest risk, keeping in mind that post-marketing data have reported rivaroxaban to be most likely associated with DILI[40]. Therefore, these data suggested that current performance of this risk stratification tool is still suboptimal. In fact, this algorithm is based on pharmacokinetics characteristics and chemical features. Based on published data, apixaban, rivaroxaban and dabigatran contain structural moieties that suggest some alerts (para-methoxyaniline and bis-anilide motifs in apixaban; chlorothiophene and bis-anilide motifs in rivaroxaban; bis-anilide motifs in dabigatran), which, however, do not seem to undergo metabolism and/or generate reactive metabolites[41,42]. In the case of rivaroxaban, the pendant chlorothiophene motif is also essential for pharmacology and cannot be replaced. The aniline structural moiety is also present in the oral direct thrombin inhibitor dabigatran, which, however is not subject to oxidative metabolism by CYP enzymes in humans[43]. In summary, only partially may these peculiarities explain the risk observed in humans for rivaroxaban. This is also emphasized by the case of ximelagatran, which does not possess structural moieties implicated in liver toxicity (dose-based risk score = 2.55; Cmax-based risk score = 1.90, according to Chen *et al*[34]), thus suggesting that additional mechanisms are likely to be implicated in DILI occurrence in humans.

Therefore, our hypothesis is that there should be additional aspects that may modify the likelihood of DILI occurrence in DOAC users. Apart from host-related factors (which are not modifiable), we propose that: (1) concomitant drug with hepatotoxic and/or interacting potential may cause a subclinical liver damage that can results in symptomatic injury in susceptible patients (a concept similar to the repolarization reserve postulated for DITdP[44]); and (2) the underlying disease for which the DOAC is prescribed may contribute in increasing the likelihood of DILI with unknown mechanisms. In fact, the

majority of published case reports occurred in surgical patients with venous thromboembolism rather than with atrial fibrillation.

This calls for monitoring of liver safety when making treatment changes (addition of drugs with recognized hepatotoxicity potential, especially for long-term use) considering the different therapeutic indications of DOACs, where their role is still incompletely defined (*e.g.,* heparin-induced thrombocytopenia, cancer, triple therapy, coronary diseases, heart failure)[45]. In the meantime, chemists, pharmacologists and clinicians should join efforts to understand drug signature subtending the mechanistic basis of DILI and establish causality.

CONCLUSION AND PERSPECTIVE

Early detection, prediction and accurate risk stratification represent an urgent need for clinicians, basic scientists, regulators and drug companies. As compared to DITdP, predictivity of pre-clinical assays for DILI is still suboptimal. The role of animal studies remains questionable, mainly because of the incomplete understanding of the mechanisms underlying DILI, as well as marked species differences in response to, and in the metabolism of, xenobiotics.

As a result, there is currently no universally accepted animal model. It seems unlikely that a single *in vitro* system will be able to mimic the complex interactions in the human liver. Three-dimensional multicellular systems together with toxicogenomics-based methodologies and next-generation sequencing technologies are promising tools to develop predictive models in the near future[46]. In particular, pluripotent stem cells, which include embryonic and induced pluripotent stem cells, are being investigated to replace human primary hepatocytes (the current gold standard for preclinical toxicological screening), because they provide a stable source of hepatocytes and can be exploited for multiple applications, including early preclinical hepatotoxicity screening[47].

Risk stratification in humans is even more challenging, especially for herbals/food supplements as well as biotechnological products, because of their unpredictable kinetics and sometimes variable content.

Case reports are of course of great importance for timely detection of safety signals, although they cannot be formally used *per se* for a reliable risk assessment and stratification, but should be integrated with other data sources such as clinical trials, cohort and case-control analyses.

The importance of this global approach in the overall assessment of drug-related toxicities is recommended by the recent Pharmacovigilance legislation, which calls for integrated risk/benefit assessment based on an integrated view of all pieces of evidence[48]. This was the case of pancreatitis with incretin-based drugs: While the signal emerged from case reports, the actual existence and the magnitude of a true association was later investigated through multiple data sources, including a recent systematic review with meta-analysis of both clinical trials and observational studies, which suggested that the incidence of pancreatitis in users of incretin-based therapy is low and that the drugs do not increase the risk of pancreatitis[49-59].

In conclusion, existing consortia should pursue a joint effort along this innovative pathway aiming to develop algorithms capable not only of discriminating hepatotoxic from non-hepatotoxic compounds, but also to differentiate the risk among agents belonging to the same therapeutic class. In particular, in the era of big data, it is important to integrate real-world information (*i.e.,* registries, healthcare databases, spontaneous reporting systems, literature) with cheminformatics in order to provide a comprehensive DILI risk score and fulfill clinicians' and patients' expectations about "primum non nocere".

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