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Drugs Associated with Hepatotoxicity and their Reporting Frequency of Liver Adverse Events in VigiBase™

Unified List Based on International Collaborative Work

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Abstract

Background: Challenges exist in the clinical diagnosis of drug-induced liver injury (DILI) and in obtaining information on hepatotoxicity in humans.
Objective: (i) To develop a unified list that combines drugs incriminated in well vetted or adjudicated DILI cases from many recognized sources and drugs that have been subjected to serious regulatory actions due to hepatotoxicity; and (ii) to supplement the drug list with data on reporting frequencies of liver events in the WHO individual case safety report database (VigiBase™).
Data Sources and Extraction: (i) Drugs identified as causes of DILI at three major DILI registries; (ii) drugs identified as causes of drug-induced acute liver failure (ALF) in six different data sources, including major ALF registries and previously published ALF studies; and (iii) drugs identified as being subjected to serious governmental regulatory actions due to their hepatotoxicity in Europe or the US were collected. The reporting frequency of adverse events was determined using VigiBase™, computed as Empirical Bayes Geometric Mean (EBGM) with 90% confidence interval for two

customized terms, 'overall liver injury' and 'ALF'. EBGM of ≥2 was considered a disproportional increase in reporting frequency. The identified drugs were then characterized in terms of regional divergence, published case reports, serious regulatory actions, and reporting frequency of 'overall liver injury' and 'ALF' calculated from VigiBase™.

Data Synthesis: After excluding herbs, supplements and alternative medicines, a total of 385 individual drugs were identified; 319 drugs were identified in the three DILI registries, 107 from the six ALF registries (or studies) and 47 drugs that were subjected to suspension or withdrawal in the US or Europe due to their hepatotoxicity. The identified drugs varied significantly between Spain, the US and Sweden. Of the 319 drugs identified in the DILI registries of adjudicated cases, 93.4% were found in published case reports, 1.9% were suspended or withdrawn due to hepatotoxicity and 25.7% were also identified in the ALF registries/studies. In VigiBase™, 30.4% of the 319 drugs were associated with disproportionally higher reporting frequency of 'overall liver injury' and 83.1% were associated with at least one reported case of ALF.

Conclusions: This newly developed list of drugs associated with hepatotoxicity and the multifaceted analysis on hepatotoxicity will aid in causality assessment and clinical diagnosis of DILI and will provide a basis for further characterization of hepatotoxicity.

Background

The recent increase in reports of serious adverse events associated with drug therapy is of important public health interest.[1] From 1998 through 2005, reported serious and fatal adverse events increased nearly 3-fold, four times faster than the increase in the total number of outpatient prescriptions during the same period.[1] Drug-induced liver injury (DILI) is one of the most common drug-related adverse events and can result in death or acute liver failure (ALF) requiring emergency liver transplant. In the US, DILI is the leading cause of ALF among those under consideration for liver transplantation.[2]

The diagnosis of DILI is challenging since the evaluation of liver histology may not be diagnostic and sensitive/specific biomarkers are still under development; thus, clinical diagnosis currently relies on comprehensive clinical assessment. The assessment of suspected DILI cases consists of two major diagnostic processes: the exclusion of other causes of liver injury and the identification of a 'signature pattern' of disease manifestations that are temporally related to initiation and discontinuation of the suspected medication(s).[3,4] Clinical suspicion of DILI and reasonable exclusion of other causes of liver injury are essential in clinical assessment. Whether the specific drug has known hepatotoxicity provides key information as to the likelihood that a given drug is responsible for the clinical picture. Evidence-based information on hepatotoxicity, however, is not readily available in a single source. In general, the product information of drugs is frequently used as a valuable source of information. Furthermore, clinicians search the medical literature for case reports involving the suspect drug. However, many DILI events are not necessarily reported in the literature and, even in reported cases, rigorous adjudication or vetting may not have been employed. Moreover, comprehensive information reflecting the 'degrees' of hepatotoxicity, e.g. frequency of events or possibility of progressing to ALF, is currently unavailable. Such comprehensive information on hepatotoxicity would greatly aid clinicians in making the correct clinical judgement in DILI

and may facilitate future evaluation of hepatotoxicity across different disciplines.

Several clinical scoring systems have been implemented since 1992 to provide a standardized causality assessment on suspected DILI cases.[3] Currently, the Roussel Uclaf Causality Assessment Method (RUCAM) [also designated the CIOMS scale] is widely used to assess the probability of DILI, although this method has limitations.[4,5] The RUCAM/CIOMS scoring system assigns weighted scores to clinical and laboratory data in seven domains: time to onset (from start and cessation of the implicated drug), time to enzyme normalization after cessation of the drug (>50% improvement), risk factors, concomitant drug use, alternative non-drug-related causes of liver injury, previous information on hepatotoxicity of the drug, and response to re-administration, which can be either intentional or accidental.[6,7] The probability of DILI (i.e. definite/highly probable, probable, possible, unlikely or excluded) is then determined based on the total scores from all the domains. The scorer's judgement is influenced by previous information regarding hepatotoxicity of the drug, concomitant hepatotoxic drug use and alternative non-drug-related causes of liver injury, which may vary among observers. The availability of comprehensive information on the hepatotoxicity of drugs at a single source could assist physicians in the evidence-based evaluation of hepatotoxicity, and eventually assist in reducing inter-observer variance in clinical causality assessment scoring systems.

The aim of this international collaborative effort is to develop a unified list that combines drugs incriminated in well vetted or adjudicated DILI cases from many recognized sources, and drugs that have been subjected to serious regulatory actions due to hepatotoxicity. This list was supplemented with data on reporting frequencies of liver events in the database of the WHO Programme for International Drug Monitoring, VigiBase™, to provide a multifaceted evidence base for the evaluation of hepatotoxicity.

Methods

We used lists of (i) drugs adjudicated as causes of DILI by study groups in Spain, Sweden and the US; (ii) drugs implicated as causes of ALF by the study groups in these three countries; and (iii) in Europe or the US, drugs that have been subjected to serious regulatory actions due to hepatotoxicity. Updated and complete drug lists were obtained from the study groups. The lists from different sources were combined. Drugs were then analyzed for differences among the different data sources and for reporting frequencies of liver events with different severities in VigiBase™.

Data Sources and Data Collection

The data sources used to identify drugs associated with hepatotoxicity include (i) databases created by ongoing prospective studies to collect cases of DILI or ALF; (ii) databases created using regulatory resources; (iii) published literature; and (iv) other public domains, including websites of the regulatory agencies. The designs and methods used in each study/study group (i.e. population selection, causality assessment and drug incrimination) are summarized in tables I and II.

Data Sources in Spain

Spanish Hepatotoxicity Registry

The Registry of Hepatotoxicity in southern Spain[8,9] was established as a collaborative network in 1994 by two of the authors of this study (RJA and MIL) to prospectively identify cases of DILI in a standardized manner and to collect detailed clinical information and biological samples. A detailed description of the operational structure of the registry, data recording and case ascertainment in this collaborative network have been reported elsewhere.[8] Briefly, the study includes all the cases of DILI identified at the registered hospitals that meet the criteria listed in table I, regardless of severity. The diagnosis of DILI is made in a standardized manner using the criteria of the International Consensus Meeting for liver injury[10] and the RUCAM/CIOMS scoring system[7] in addition to clinical judgement by experienced hepatologists. Only cases considered drug-related by experts' clinical judgements were assessed by the RUCAM/CIOMS scoring system. Of these, only cases assessed as definite or highly probable, probable or possible

Table I. Summary of data sources: study population and causality assessment in the three drug-induced liver injury (DILI) registries

Characteristic	Spain: hepatotoxicity registry	Sweden: DILI with jaundice	US: DILIN
Authors/principal investigators	Andrade RJ, Lucena MI	Björnsson E	Watkins P
Data sources	Multicentre	Swedish Adverse Drug Reactions Advisory Committee	Multicentre
Year	1994–2008[a]	1970–2004	2003–2007[a]
Population	DILI	DILI	DILI
inclusion criteria	ALT >2×ULN or conjugated Bil >2×ULN, or combined increase in AST, AP and T. Bil, with one of these >2×ULN	Bil >2×ULN	1. AST or ALT >5×ULN/BL or AP >2×ULN/BL on two consecutive measures 2. T. Bil >2.5 mg/dL, with ALT, AST, or AP ↑ 3. INR >1.5 with ALT, AST or AP ↑
exclusion criteria	Other causes of liver disease	Paracetamol (acetaminophen)	Paracetamol, pre-existing liver disease[b]
no. of subjects	650	784	300
Causality assessment			
expert opinion	Yes	No	Yes
RUCAM/CIOMS	Yes	Yes	Yes

a Studies are ongoing.

b With the exception of hepatitis C and B, and non-alcoholic fatty liver disease.

AP = alkaline phosphatase; **Bil** = bilirubin; **DILIN** = DILI network; **INR** = international normalized ratio; **RUCAM** = Roussel Uclaf Causality Assessment Method; **T.Bil** = total bilirubin; **ULN** = upper limit of normal; **ULN/BL** = ULN or pretreatment baselines if baseline levels are abnormal; ↑ indicates increased.

are included in the database. For identification of responsible drugs, a thorough check for present and previous use of drugs, herbal remedies and over-the-counter medications is done in each case. Information regarding drug use is obtained by asking patients, and family members if necessary, and obtaining medication containers or a written medication plan, when available. To date, more than 600 adjudicated DILI cases have been collected in the database.[11] An updated drug list from a total of 650 cases, including unpublished data, was provided for this study.

Among the DILI cases in the Spanish Hepatotoxicity Registry, the drugs implicated as causes of ALF (i.e. presence of acute deterioration of liver function tests accompanied with icterus, coagulopathy and encephalopathy leading to death or liver transplantation) were also analyzed separately by combining with drugs implicated in other ALF studies/study groups.

ALF Study Conducted in Spain

Drugs implicated as causes of ALF in Spain were retrieved from previously published literature[12] and personal communication with one of the authors (AM) for further information. Detailed study designs and methods were described in the literature.[12] Briefly, 267 cases of ALF were collected at 27 hospitals in Spain, from 1 January 1992 to 31 December 2000, regardless of age and aetiologies, using the standardized criteria: acute, life-threatening deterioration of liver function in the absence of pre-existing liver disease, the presence of jaundice, impairment in liver function determined by the prothrombin time (prothrombin index <40% or international normalized ratio [INR] of prothrombin time ≥1.5) and encephalopathy. Aetiological diagnoses were made by experienced hepatologists at each study centre based on clinical judgements. No standardized causality assessment tool was used.

Data Sources in Sweden

Swedish Adverse Drug Reactions Advisory Committee Database

Since 1975, it has been mandatory in Sweden to report fatal, serious or new/unknown drug reactions to the Swedish Adverse Drug Reactions

Table II. Summary of data sources: study population and causality assessment in the acute liver failure (ALF) studies/study groups

Characteristic	Spain		Sweden		US	
	hepatotoxicity registry	ALF study	fatal DILI or DILI with liver transplantation	Sweden ALF study	ALF Study Group	ALF/UNOS study
Authors/principal investigators	Andrade R, Lucena I	Escorsell A	Björnsson E	Wei G	Lee WM	Russo MW
Data sources	Multicentre	Multicentre	Swedish Adverse Drug Reactions Advisory Committee	Multicentre	Multicentre	UNOS
Year	1994–2008[a]	1992–2000	1966–2002	1994–2003	1996–2008[a]	1990–2002
Population	ALF-DILI	ALF	ALF-DILI	ALF	ALF	ALF
inclusion criteria	Presence of acute deterioration of liver function tests accompanying icterus, coagulopathy and encephalopathy leading to death or liver transplantation	1. Jaundice 2. PI <40% or INR ≥1.5 3. Encephalopathy	1. Fatal or liver transplant cases	1. INR >1.5	1. PT >15 sec or INR ≥1.5 2. Encephalopathy 3. Within 26 wk	1. Liver transplant candidates 2. Acute hepatic necrosis from drugs 3. At least one follow-up after transplant 4. UNOS status 1 5. Specific drug was listed
exclusion criteria	Other causes of liver disease	Pre-existing liver diseases			Pre-existing liver disease	1. Other aetiology of acute hepatic necrosis 2. Previous liver transplant
no. of subjects	23 of 650	52 of 267	103	160[b] of 279	132[c] of 1400[d]	270
Causality assessment						
expert opinion	Yes	Yes	No	Yes	Yes	Yes
RUCAM/CIOMS	Yes	No	Yes	No	No	No

a Studies are ongoing.

b 118 were paracetamol (acetaminophen)-induced and 42 were idiosyncratic.

c Idiosyncratic (non-paracetamol cases).

d At the time the data were collected.

DILI = drug-induced liver injury; **INR** = international normalized ratio; **PI** = prothrombin index; **PT** = prothrombin time; **RUCAM** = Roussel Uclaf Causality Assessment Method; **UNOS** = United Network for Organ Sharing.

Advisory Committee (SADRAC). All reports of suspected DILI received by the SADRAC between 1970 and 2004 have been computerized and are available online for legally acceptable users with a password. There is no standardized report form for this reporting; however, full medical records, including results of laboratory tests, imaging studies, biopsies and autopsies, are requested for all fatal cases and for the majority of serious cases. The opinion of an expert hepatologist with extensive experience in DILI is requested in difficult assessments. This assessment is based on clinical judgement, not on any published method for assessment of causality.

Using the above database, a data set of severe DILI (serum bilirubin ≥2× the upper limit of normal [ULN]) has been aggregated (from 1970 to 2004)[13] using the RUCAM/CIOMS score[7] as a standardized causality assessment. This dataset includes 784 severe DILI cases with possible, probable or highly probable relationship on the RUCAM/CIOMS score after excluding paracetamol (acetaminophen)-associated liver injury (n = 12).[13]

A separate dataset of fulminant drug-induced hepatic failure (fatal or liver transplant cases) has been aggregated (from 1966 to 2002)[14] using the RUCAM/CIOMS score,[7] which was also used in the present study as one of the data sources for drug-induced ALF cases.

ALF Study Conducted in Sweden

Another published study from Sweden that investigated the aetiology and outcome of ALF from ten university hospitals in Sweden (from 1994 to 2003)[15] was also used as a data source. In the study, the aetiology of each ALF case was determined by the hepatologists at each university hospital.

Data Sources in the US

Drug-Induced Liver Injury Network (DILIN)

The DILIN is an ongoing, multicentre, observational study established in 2003 by the National Institute of Health (NIH). Detailed study design and methods are described in the published literature.[16,17] Briefly, patients (≥2 years of age) are enrolled in this ongoing study if there is a strong clinical suspicion that a liver injury event was caused by a medication or herbal agent occurring within 6 months before enrolment. Patients must meet one of the following biochemical criteria for enrolment into this study: (i) AST or ALT level >5× ULN (or pretreatment baseline if baseline level is abnormal), or alkaline phosphatase level >2× ULN (or pretreatment baseline if baseline level is abnormal) on two consecutive occasions; (ii) total serum bilirubin level >2.5 mg/dL along with elevated AST or ALT or alkaline phosphatase; or (iii) INR >1.5 with elevated AST or ALT or alkaline phosphatase level. Known or suspected paracetamol toxicity is excluded. Patients with underlying hepatitis C virus, hepatitis B virus or nonalcoholic fatty liver disease are eligible if they developed superimposed DILI; however, those with other types of underlying chronic liver disease (e.g. autoimmune liver disease, sclerosing cholangitis) are excluded.

The causality assessment on each enrolled case is based on two different causality instruments: the widely used RUCAM/CIOMS score[7] and by assigning a DILIN causality score based on the consensus of at least three hepatologist members of the committee.[18] The DILIN causality score categorizes the strength of causal association between the implicated agent and the liver injury event as definite (>95% likelihood), highly likely (75–95%), probable (50–74%), possible (25–49%) and unlikely (<25%). In the present study, we used drugs that were incriminated as 'possible' or higher.

The drugs identified as causes of DILI in the 300 patients enrolled in the DILIN between September 2004 and December 2007 were retrieved from the recently published study.[16]

ALF Study Group

Initiated in 1996, the ALF Study Group (ALFSG)[19] is a 24-centre consortium funded by the NIH to prospectively enrol adult patients with ALF to describe their aetiology, clinical features and outcomes. The ALFSG has accumulated over 1500 cases and is managed at the data coordination centre at the University of Texas Southwestern Medical Center, Dallas.[20] ALF was defined as the onset of coagulopathy and encephalopathy within 26 weeks of illness onset in a patient without pre-existing liver disease.[19,20] Aetiological diagnoses were made by participating

experienced hepatologists at each study centre, based on clinical judgements; no standardized causality assessment tool was used. The list of the drugs implicated as causes of ALF in the enrolled patients was obtained from the data coordinating centre. In cases in which more than one drug was reported as a possible cause of ALF, all drugs were extracted and listed in the present study.

ALF Study Conducted in the US Using United Network for Organ Sharing Liver Transplant Database

A study in the US using the United Network for Organ Sharing Liver Transplant Database was also used as a data source in this study.[2] The study identified 270 drug-induced ALF cases in the database between 1990 and 2002. Aetiologies and drug incrimination in these cases were based on the information reported in the database.

Evaluation of Drugs Subjected to Serious Regulatory Actions due to Hepatotoxicity

In the US or Europe, drugs subjected to serious regulatory actions, either suspension (i.e. temporary withdrawal of marketing registration or the use of special prescription form pending prompt commencement of formal or amended license) or withdrawal (i.e. indefinite removal of a drug from the marketplace), primarily due to hepatotoxicity, were identified using the public domains and published literature. Furthermore, the information was obtained via personal communications with EU and US regulatory affairs at GlaxoSmithKline. Our primary reason to include this information was to evaluate drugs associated with hepatotoxicity from a different perspective. Regulatory actions due to safety concerns reflected various factors, i.e. incidence and severity of hepatotoxicity, availability of alternative treatments and benefit-risk ratio. In some cases, manufacturers pursue early action for safety reasons. To comply with our primary purpose, the information on such safety actions made by manufacturers in communication with regulatory agencies was also included in this study.

In Europe

Drugs withdrawn in Europe between 1960 and 1999, primarily due to hepatotoxicity, were collected through published papers.[21-23] Further information was sought through the public domain,[24] as well as personal communication with Regulatory Affairs, GlaxoSmithKline.

In the US

To identify all the drugs resulting in suspension or withdrawal in the US primarily due to hepatotoxicity, all the Safety Alerts for Human Medical Products (Drugs, Biologics, Medical Devices, Special Nutritionals and Cosmetics) in the MedWatch Product Safety Information from 1996 to 2008 (http://www.fda.gov/medwatch/safety.htm) were searched for liver-related key words (i.e. liver, hepatic, hepatotoxicity and hepatotoxic) and reviewed for serious regulatory actions, suspension or withdrawal due to hepatotoxicity. Published literature[21-23,25] and the public domain[24] were also referred to in order to identify drugs that were suspended or withdrawn in the US.

Published Literature of DILI

Publications reporting DILI related to drugs identified in this study were identified using PubMed and other publicly available search engines (e.g. Google™, Google™ Scholar), as well as a publication that provides periodic updates of the literature on hepatotoxic drugs.[26] All case reports were included in the analysis, regardless of whether standardized causality assessments were used. Terms used for this search include the combination of drug names and liver terms (e.g. drug-induced liver injury, liver injury, liver, hepatotoxicity, aminotransferase, cholestasis and/or cholestatic).

VigiBase™

The global individual case safety report (ICSR) database system,[27] VigiBase™, was used to obtain reporting frequencies of the liver events related to the drugs identified in this study. The WHO International Drug Monitoring Programme started in 1968 and is currently developed and maintained by the Uppsala Monitoring Centre (UMC), Uppsala, Sweden, on behalf of the WHO. The database holds more than 5 million ICSRs since 1968 from more than 80 countries worldwide, and has been used as a data source for DILI research.[28] The majority of ICSRs in the database were received from Europe and North

America, and include both regulatory and voluntary sources of reporting, depending on each country's pharmacovigilance system.

Some of the drugs are identified by more than one name (i.e. generic and brand name) in the WHO database. In such cases (e.g. amoxicillin/clavulanic acid), data were combined and analysed as pooled data.

Statistical Analysis

The reporting frequency data in VigiBase™ were calculated as Empirical Bayes Geometric Mean (EBGM) with 90% CI using the Multi-Item Gamma Poisson Shrinker (MGPS) method as previously reported.[29-31] MGPS is an empirical Bayes data-mining method that uses all of the data on drugs and events in a particular database to detect safety signals.[30,32] For each drug-event pair observed in a database, MGPS computes internal expected counts using a stratified full independence model, and derives the EBGM and associated two-sided 90% CI (EB05, EB95). EBGM is conceptually similar to the proportional reporting ratio,[33] and EBGM values represent relative reporting rates (after Bayesian smoothing) for drug-event pairs in a given database. Briefly, an EBGM of 5 is interpreted to mean that a drug-event pair has been reported five times as frequently as would be expected if reports involving the drug and reports of the event were independent (i.e. no association).

To compute EBGM values, we defined two customized liver terms with different severity: (i) 'overall liver injury'; and (ii) 'ALF' (http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4266b1-02-06-FDA-appendic-f.pdf), using groups of 'Preferred Terms' from the Medical Dictionary for Regulatory Activities (MedDRA®) coding system (see table S1, Supplemental Digital Content 1, http://links.adisonline.com/DSZ/A27). The EBGMs were calculated as a cumulative reporting frequency from 1968 to 2008. The total number of any cases reported with a drug, and number of cases reported with the drug and liver events, were also retrieved from the same time period. We considered EBGM of ≥2 as a disproportional increase in reporting frequency.

Results

Drugs Identified as Causes of Liver Injury at the Three DILI Registries

Overall, 369 drugs were identified in the three DILI registries as causes of liver injury. Among the 369 drugs, 50 drugs (13.6%) classified as herbal medicines, dietary supplements or alternative medicines were set aside for future investigation and excluded from this analysis, leaving 319 pharmaceuticals. Drugs identified as a cause of liver injury in five or more cases in the three registries (76 drugs) are presented in table III (the complete drug list is provided in table S2, Supplemental Digital Content).

Drugs identified at the three sites showed regional divergence. Thirty-one drugs (9.7%) were identified in all three registries. Concordance of the identified drugs was higher between European registries (28.7% or 73/254 for Spanish vs Swedish registries) compared with US vs European registries (18.2% or 44/242 for the Swedish registry vs DILIN, and 21.8% or 55/252 for the Spanish registry vs DILIN).

The number of identified cases for each suspect drug at the three registry sites also varied. Table IV presents frequently identified drugs at each registry site with numbers of identified cases (including top ten rankings at each site). Drugs frequently identified in the combined drug list (table IV) were (in descending order, more than 30 cases only): amoxicillin/clavulanic acid (n = 136), diclofenac (n = 38), cotrimoxazole (n = 34), isoniazid (n = 31) and disulfiram (n = 31). Flucloxacillin (n = 129) and erythromycin (n = 48) were also frequently identified, but not consistently among the three sites. Flucloxacillin, erythromycin and disulfiram were notably prevalent in the Swedish registry, while in the Spanish registry and DILIN, amoxicillin/clavulanic acid was the most prevalent (n = 105 in Spain; n = 26 in the US). In the US, nitrofurantoin (n = 18) was also prevalent, but not in the other registries. Furthermore, flutamide, ibuprofen, fluvastatin and the combination therapy for tuberculosis (i.e. rifampicin [rifampin]-isoniazid-pyrazinamide) were notably prevalent in the Spanish registry.

Table III. Drugs identified in five or more adjudicated drug-induced liver injury (DILI) cases at the three DILI registries and corresponding reporting frequency data in VigiBase™

Generic name	DILI registries			No. of cases in the WHO database and EBGM				
	Spanish registry	Swedish registry	DILIN (US)	total no. of reports	'overall liver injury'		'acute liver failure'	
					no.	EBGM (90% CI)[a]	no.	EBGM (90% CI)[a]
Allopurinol	3	2	3	10 125	990	2.1 (2.0, 2.3)	54	2.1 (1.7, 2.7)
Amiodarone	4	1	3	15 144	1 456	2.2 (2.1, 2.3)	131	3.1 (2.7, 3.6)
Amlodipine	1	1	3	14 194	407	0.7 (0.7, 0.8)	11	0.3 (0.2, 0.4)
Amoxicillin	6	1	2	30 936	598	0.5 (0.5, 0.6)	36	0.5 (0.4, 0.7)
Amoxicillin/clavulanic acid[b]	105	5	26	20 761	3 471	4.3 (4.2, 4.4)	85	1.6 (1.3, 1.9)
Aspirin (acetylsalicylic acid)	4	1	0	27 384	720	0.6 (0.6, 0.7)	59	0.8 (0.6, 1.0)
Atorvastatin	9	3	4	23 176	2 694	3.0 (2.9, 3.1)	139	1.8 (1.6, 2.1)
Azathioprine	8	4	0	5 619	998	4.2 (4.0, 4.4)	35	2.1 (1.6, 2.8)
Azithromycin	2	0	6	10 577	626	1.8 (1.7, 1.9)	68	2.3 (1.9, 2.8)
Bentazepam	8	0	0	48	9	2.9 (1.6, 4.8)		
Captopril	6	3	0	20 470	643	0.7 (0.6, 0.7)	29	0.8 (0.6, 1.0)
Carbamazepine	7	16	1	28 124	2 858	2.6 (2.5, 2.6)	142	2.2 (1.9, 2.5)
Cefuroxime	3	2	1	8 443	338	1.1 (1.0, 1.2)	8	0.5 (0.3, 0.8)
Chlorpromazine	3	8	0	6 291	1 076	4.0 (3.8, 4.2)	15	1.2 (0.8, 1.8)
Ciprofloxacin	4	7	7	19 915	1 213	1.4 (1.4, 1.5)	89	1.7 (1.5, 2.1)
Clomethiazole	5	0	0	802	51	1.4 (1.1, 1.7)	2	0.9 (0.3, 2.2)
Clomipramine	0	7	0	6 469	513	2.0 (1.9, 2.1)	7	0.5 (0.3, 0.9)
Clopidogrel	4	1	0	9 801	280	0.7 (0.7, 0.8)	22	0.7 (0.5, 0.9)
Cloxacillin	4	3	0	7 593	148	0.5 (0.4, 0.6)	3	0.2 (0.1, 0.4)
Cotrimoxazole[b]	2	22	10	46 689	2 265	1.2 (1.2, 1.2)	100	1.0 (0.9, 1.2)
Cyclophosphamide	0	5	4	12 317	598	1.2 (1.1, 1.3)	82	2.3 (1.9, 2.7)
Diclofenac	16	19	3	29 178	2 051	1.6 (1.6, 1.7)	104	1.5 (1.3, 1.8)
Disulfiram	1	27	3	1 551	365	5.1 (4.7, 5.6)	48	14.6 (11.4, 18.4)
Doxycycline	0	4	4	9 149	359	1.0 (0.9, 1.1)	24	1.1 (0.8, 1.6)
Duloxetine	0	0	6	6 691	688	2.6 (2.5, 2.8)	37	1.2 (0.9, 1.6)
Ebrotidine	21	0	0	77	67	19.5 (15.9, 23.8)	2	1.7 (0.5, 4.3)
Enalapril	4	8	0	28 147	706	0.6 (0.5, 0.6)	31	0.5 (0.4, 0.7)
Erythromycin	6	42	0	16 436	2 514	4.0 (3.9, 4.1)	27	0.9 (0.6, 1.2)
Ethinylestradiol/levonorgestrel[b]	2	8	0	14 793	563	1.2 (1.1, 1.3)	7	0.3 (0.1, 0.5)
Fenofibrate	6	0	2	3 361	594	4.0 (3.7, 4.3)	14	1.3 (0.8, 1.9)
Flucloxacillin (floxacillin)	0	129	0	4 261	1 470	8.0 (7.7, 8.4)	19	1.7 (1.2, 2.5)
Fluconazole	1	1	3	7 049	884	3.4 (3.2, 3.6)	84	4.5 (3.7, 5.3)

Continued next page

Table III. Contd

Generic name	DILI registries			No. of cases in the WHO database and EBGM				
	Spanish registry	Swedish registry	DILIN (US)	total no. of reports	'overall liver injury'		'acute liver failure'	
					no.	EBGM (90% CI)[a]	no.	EBGM (90% CI)[a]
Flutamide	22	4	0	2 834	727	5.3 (5.0, 5.7)	106	13.4 (11.4, 15.7)
Fluvastatin	10	0	1	3 758	714	4.4 (4.2, 4.7)	14	1.1 (0.7, 1.7)
Halothane	2	15	0	2 409	1 722	16.7 (16.0, 17.3)	194	50.6 (44.9, 56.9)
Ibuprofen	21	6	1	29 931	880	0.8 (0.7, 0.8)	83	1.2 (1.0, 1.4)
Interferon-β-1a	0	0	5	2 486	182	2.0 (1.8, 2.2)	14	1.4 (0.9, 2.2)
Isoniazid	11	7	13	8 582	2 487	6.7 (6.4, 6.9)	140	7.8 (6.7, 9.0)
Isoniazid-rifampicin	5	0	0	NA	NA	NA	NA	NA
Lamotrigine	0	1	6	12 902	652	1.3 (1.2, 1.4)	80	1.7 (1.4, 2.1)
Leflunomide	4	0	4	5 261	716	3.7 (3.5, 4.0)	55	3.3 (2.6, 4.0)
Levofloxacin	5	0	10	9 953	448	1.1 (1.1, 1.2)	66	1.9 (1.6, 2.3)
Lisinopril	0	3	2	17 600	378	0.5 (0.4, 0.5)	21	0.5 (0.3, 0.6)
Lovastatin	3	0	3	13 105	2 088	3.6 (3.5, 3.7)	36	1.4 (1.0, 1.8)
Mercaptopurine	0	0	6	1 026	214	5.6 (5.0, 6.3)	14	3.3 (2.1, 5.0)
Mianserin	1	5	0	4 855	534	2.4 (2.3, 2.6)	3	0.3 (0.1, 0.7)
Minocycline	2	0	4	6 867	696	2.7 (2.5, 2.8)	12	0.8 (0.5, 1.3)
Naproxen	2	12	0	23 545	667	0.6 (0.6, 0.7)	54	0.9 (0.7, 1.1)
Nefazodone	1	4	0	8 414	752	2.6 (2.4, 2.7)	94	4.2 (3.5, 4.9)
Nimesulide	9	0	0	1 500	350	5.5 (5.0, 6.0)	23	4.0 (2.8, 5.6)
Nitrofurantoin	1	4	18	10 854	1 138	2.6 (2.4, 2.7)	74	3.6 (3.0, 4.4)
Norfloxacin	4	2	0	6 215	311	1.2 (1.1, 1.3)	12	0.8 (0.5, 1.3)
Omeprazole	5	6	0	23 317	1 172	1.2 (1.2, 1.3)	72	1.2 (0.9, 1.4)
Paracetamol (acetaminophen)[b]	20	0	0	29 636	4 481	4.4 (4.3, 4.5)	1 072	14.2 (13.5, 14.9)
Paracetamol and dextropropoxyphene	0	7	0	3 386	743	5.1 (4.8, 5.4)	18	2.0 (1.3, 2.8)
Paroxetine	7	1	1	40 445	816	0.6 (0.5, 0.6)	48	0.4 (0.3, 0.5)
Phenytoin	3	1	9	20 165	1 503	1.8 (1.7, 1.9)	119	2.4 (2.0, 2.8)
Piroxicam	5	0	0	17 017	565	0.7 (0.7, 0.8)	23	0.7 (0.5, 1.0)
Ranitidine	3	10	2	17 700	1 372	1.8 (1.7, 1.9)	30	0.8 (0.6, 1.1)
Rifampicin (rifampin)	1	2	2	7 858	2 532	7.5 (7.2, 7.7)	126	6.5 (5.5, 7.5)
Rifampicin-isoniazid-pyrazinamide	19	0	0	NA	NA	NA	NA	NA
Sertraline	2	2	1	31 888	785	0.7 (0.7, 0.7)	50	0.6 (0.5, 0.7)
Simvastatin	6	3	3	25 366	2 503	2.3 (2.3, 2.4)	92	1.2 (1.0, 1.5)
Sodium aurothiomalate	1	4	0	1 806	131	1.6 (1.4, 1.8)	3	0.8 (0.3, 1.7)
Stanozolol	5	0	0	342	73	4.2 (3.5, 5.1)	1	0.8 (0.2, 2.6)

Continued next page

Table III. Contd

Generic name	DILI registries			No. of cases in the WHO database and EBGM				
	Spanish registry	Swedish registry	DILIN (US)	total no. of reports	'overall liver injury'		'acute liver failure'	
					no.	EBGM (90% CI)[a]	no.	EBGM (90% CI)[a]
Sulfasalazine	2	7	0	7 157	867	2.8 (2.7, 3.0)	46	2.8 (2.2, 3.6)
Sulindac	0	7	0	5 699	747	2.8 (2.6, 3.0)	19	1.9 (1.3, 2.6)
Telithromycin	0	0	6	2 603	422	5.0 (4.6, 5.4)	50	5.6 (4.4, 7.2)
Terbinafine	2	6	4	14 123	1 181	2.0 (1.9, 2.1)	35	0.9 (0.7, 1.1)
Tetrabamate	7	0	0	NA	NA	NA	NA	NA
Thiamazole	5	7	0	2 005	306	3.8 (3.5, 4.2)	6	1.1 (0.6, 2.1)
Ticlopidine	13	7	0	8 670	1 385	3.5 (3.3, 3.6)	27	1.1 (0.8, 1.5)
Trimethoprim	1	5	1	6 114	177	0.7 (0.6, 0.8)	5	0.4 (0.2, 0.8)
Trovafloxacin	5	0	0	3 877	596	4.5 (4.2, 4.8)	100	9.4 (7.8, 11.2)
Valproic acid	9	2	7	23 592	2 429	2.8 (2.7, 2.9)	349	6.0 (5.5, 6.5)
Verapamil	2	2	1	12 682	622	1.1 (1.1, 1.2)	26	1.0 (0.7, 1.4)

a EBGM of the proportional reporting ratio with 90% CI.

b Pooled data. For 'paracetamol', seven different compounds containing paracetamol were combined.

DILIN = DILI network; **EBGM** = Empirical Bayes Geometric Mean; **NA** = not available.

Among the 319 drugs identified at the three registries, 298 (93.4%) have been published as a cause of liver injury and 6 (1.9%) have been suspended or withdrawn due to hepatotoxicity, either in the US or Europe. The reporting frequency of liver events in the WHO database is also shown in table III. Among the 319 identified drugs, 97 (30.4%) were associated with disproportionally higher reporting frequency of 'overall liver injury' compared with the expected frequency (EBGM ≥2). Of the 319 drugs, 265 (83.1%) were associated with at least one reported case of 'ALF'. Some drugs were more strongly associated with 'ALF' than 'overall liver injury' (with an EBGM for 'ALF' more than twice that for 'overall liver injury' events); such drugs included halothane, desflurane, isoflurane, enflurane, paracetamol, cyproterone, disulfiram, flutamide, valproic acid, didanosine and trovafloxacin. By contrast, methyltestosterone, albendazole, bentazepam, josamycin, calcium carbimide and succimer (dimercaptosuccinic acid or DMSA) were associated with disproportionally higher reporting frequency of 'overall liver injury' events (EBGM ≥2), but had no reported cases of ALF in the WHO database. Overall, 32.2% of drugs reported as a cause of liver injury in the published literature exhibited an EBGM ≥2, compared with only 4.8% for drugs not reported as a cause of liver injury in the published literature. Five of the six drugs (83.3%) suspended or withdrawn due to hepatotoxicity, either in the EU or US, were found in the WHO database, and all five drugs were associated with disproportionally higher reporting frequency of 'overall liver injury' (EBGM ≥2), with an average EBGM of 8.7, while 283 of the 313 drugs (90.4%) that were not suspended or withdrawn due to hepatotoxicity were found in the database, and 92 of these drugs (32.5%) were associated with disproportionally higher reporting frequency of 'overall liver injury', with an average EBGM of 2.0.

Drugs Subject to Serious Regulatory Actions in the US or Europe

Forty-seven drugs were suspended or withdrawn primarily due to hepatotoxicity in the US (n = 13) or Europe (n = 45). Drugs suspended or

withdrawn [21-24] due to other (primary) reasons (but also exhibiting hepatotoxicity) were not included in this analysis. These included amineptine (dependence), amodiaquine (agranulocytosis), glafenine (severe allergic reactions), chlormezanone (severe cutaneous reactions), sulfacarbamide (renal, dermatological and hematological reactions) and zimeldine (hypersensitivity, neurological reaction).

The 47 drugs suspended or withdrawn due to hepatotoxicity in the US or Europe are listed in table S3 of the Supplemental Digital Content. Among the 47 drugs, 45 were marketed in at least one European country, while only 16 were marketed in the US. Fourteen drugs were available both in the US and Europe. Among these, 11 were suspended or withdrawn both in the US and Europe. Another three drugs (tolcapone,

Table IV. Comparison of the number of cases for the 31 most frequently incriminated drugs among the three drug-induced liver injury (DILI) registries[a]

Generic name	Total no. of cases	Spanish registry (n = 650)	Swedish registry (n = 784)	DILIN [US] (n = 300)
Amoxicillin/clavulanic acid	136	105	5	26
Flucloxacillin (floxacillin)	129	0	129	0
Erythromycin	48	6	42	0
Diclofenac	38	16	19	3
Cotrimoxazole	34	2	22	10
Isoniazid	31	11	7	13
Disulfiram	31	1	27	3
Ibuprofen	28	21	6	1
Flutamide	26	22	4	0
Carbamazepine	24	7	16	1
Nitrofurantoin	23	1	4	18
Ebrotidine	21	21	0	0
Paracetamol (acetaminophen)	20	20	0[b]	0[b]
Ticlopidine	20	13	7	0
Rifampicin [rifampin]-isoniazid-pyrazinamide	19	19	0	0
Valproic acid	18	9	2	7
Ciprofloxacin	18	4	7	7
Halothane	17	2	15	0
Ranitidine	15	3	10	2
Levofloxacin	15	5	0	10
Naproxen	14	2	12	0
Phenytoin	13	3	1	9
Enalapril	12	4	8	0
Chlorpromazine	11	3	8	0
Fluvastatin	11	10	0	1
Ethinylestradiol-levonorgestrel	10	2	8	0
Azithromycin	8	2	0	6
Lamotrigine	7	0	1	6
Mercaptopurine	6	0	0	6
Telithromycin	6	0	0	6
Duloxetine	6	0	0	6

a Includes top ten rankings at each site in descending order of the total number of cases.

b Paracetamol-liver injury was excluded from these two registries.

DILIN = DILI network.

alatrofloxacin and trovafloxacin) were suspended or withdrawn in Europe, while in the US, the product information for these three drugs included either restricted indications or a 'black-box' warning. Based on our search, several drugs other than the three mentioned above are still available elsewhere (e.g. benzarone, iproniazid, fipexide, moxisylyte, nimesulide, nialamide and tolcapone). By therapeutic class, analgesics were the most prevalent (11 drugs), followed by antidepressants (6 drugs).

Only six drugs (12.8%) of the 47 drugs were included in the list of drugs identified in all three DILI registries (see previous section). Forty (85.1%) were reported as causes of hepatotoxicity in the published literature, 30 (63.8%) were reported in the WHO database as being associated with at least one liver injury case, and 25 (83.4%) were associated with disproportionally higher reporting frequency of 'overall liver injury' compared with the expected frequency (EBGM ≥2). Twenty-five drugs (53.2%) were reported in the WHO database as being associated with at least one ALF case.

Drugs Implicated as a Cause of ALF in the ALF Registries/Studies

Overall, 122 drugs were implicated as causes of drug-induced ALF in the six different data sources of drug-induced ALF. After excluding 15 herbal substances or supplements, 107 pharmaceuticals were analysed in this study: 65 drugs in the US, 59 in Sweden and 21 in Spain (table V). Among the 107 pharmaceuticals, 62 drugs were identified in adjudicated drug-induced ALF cases either in Spain or Sweden, using the RUCAM/CIOMS scoring system.

Regional divergence of implicated drugs in the ALF cases was apparent. Only 9 drugs (8.4%) were implicated in all three countries (13 in both the US and Spain, 9 in both Spain and Sweden, and 25 in both the US and Sweden).

Of the 107 drugs implicated as a cause of ALF, 6 (5.6%) were associated with serious regulatory actions (suspension or withdrawn) either in the US or Europe, 82 (76.6%) were identified in the three DILI registries and 102 (95.3%) have been reported in the published literature as being a cause of liver injury. 104 drugs (97.2%) were reported in the WHO database as being associated with at least one liver injury case, and 101 drugs (94.4%) were reported as being associated with at least one ALF case. Among these, 52 (50%) were associated with a disproportionally higher reporting frequency of liver injury events (44 drugs [43.6%] for ALF) compared with the expected frequency (EBGM ≥2).

Discussion

A current and comprehensive list of drugs associated with hepatotoxicity was created by uniting clinical DILI information from diverse sources. This unified list includes the drugs implicated as causes of hepatotoxicity in adjudicated or well vetted cases by several studies/study groups and the drugs resulting in serious regulatory actions due to hepatotoxicity. The list was further linked to the reporting frequency data of liver injury and ALF using Vigibase™. This multifaceted analysis on hepatotoxicity revealed several important findings, which provide a basis for potential future investigation.

The VigiBase™ data resource was used to associate the drugs identified as causes of hepatotoxicity with reporting frequency of liver safety events ('overall liver injury' and 'ALF'). There are several well known inherent limitations in the usage of the reporting frequency data in pharmacovigilance systems. The limitations include reporting bias, quality of data and confounding effects by co-medications and/or other reported adverse events. A high relative reporting rate does not necessarily indicate a high incidence of the event or suggest a causal relationship between the drug and the event[33] since the values can be influenced by reporting bias, reporting frequency of other events (e.g. liver vs kidney and skin events) and frequently used co-medications. For instance, pharmacovigilance data are subject to influence by awareness of adverse events (i.e. reporting bias) through publication of cases and reports of regulatory actions. In agreement, our analysis showed that the presence of case reports or serious regulatory actions among the hepatotoxic drugs identified in this project was associated

Table V. Drugs implicated as causes of acute liver failure (ALF) in the three different countries

Generic name	US	Sweden	Spain	Adjudicated/RUCAM case[a]
Abacavir	Yes	No	No	No
Allopurinol	Yes	No	No	No
Amfetamine[b]	Yes	Yes	Yes	Yes
Amiloride	No	Yes	No	Yes
Amineptine	No	No	Yes	Yes
Aminosalicylic acid	No	Yes	No	Yes
Amiodarone	No	Yes	No	No
Amoxicillin/clavulanic acid	Yes[c]	No	Yes	Yes
Asparaginase	Yes	No	No	No
Aspirin (acetylsalicylic acid)	No	Yes	No	Yes
Atenolol	No	Yes	No	Yes
Atorvastatin	Yes	Yes	No	Yes
Azithromycin	Yes	No	No	No
Bleomycin	No	Yes	No	Yes
Bromfenac	Yes	No	No	No
Bupropion	Yes	No	No	No
Butorphanol	Yes	No	No	No
Calcium carbimide	No	No	Yes	Yes
Captopril	No	Yes	No	Yes
Carbamazepine	Yes	Yes	Yes	Yes
Cefadroxil	No	Yes	No	No
Cefepime	Yes	No	No	No
Cerivastatin	Yes	No	No	No
Chlormezanone	No	Yes	No	Yes
Chlorpromazine	No	Yes	No	Yes
Ciprofloxacin	Yes	Yes	No	Yes
Clarithromycin	Yes	No	No	No
Cocaine	Yes	Yes	No	No
Cotrimoxazole	Yes	Yes	No	Yes
Cyclophosphamide	No	Yes	No	Yes
Dapsone	Yes	Yes	No	Yes
Dextropropoxyphene	No	Yes	No	Yes
Diclofenac	Yes	Yes	No	Yes
Dicloxacillin	No	Yes	No	Yes
Didanosine	Yes	No	No	No
Disulfiram	Yes	Yes	No	Yes
Doxycycline	Yes	Yes	Yes	Yes
Ebrotidine	No	No	Yes	Yes
Enalapril	No	Yes	No	Yes
Erythromycin	No	Yes	No	Yes
Ethambutol	Yes[d]	Yes	No	Yes
Etodolac	Yes	No	No	No
Ezetimibe	Yes	No	No	No
Felodipine	No	Yes	No	Yes

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Table V. Contd

Generic name	US	Sweden	Spain	Adjudicated/RUCAM case[a]
Fialuridine	Yes	No	No	No
Flucloxacillin (floxacillin)	No	Yes	No	Yes
Fluorouracil	No	Yes	No	Yes
Fluoxetine	Yes	Yes	No	No
Flutamide	No	No	Yes	Yes
Gemtuzumab	Yes	No	No	No
Halothane	Yes	Yes	Yes	Yes
Hydralazine	Yes	Yes	No	No
Hydrochlorothiazide	No	Yes	No	Yes
Hydrocodone	Yes	No	No	No
Ibuprofen	Yes	Yes	Yes	Yes
Indometacin	No	Yes	No	Yes
Interferon-β	Yes	No	No	No
Isoflurane	Yes	No	No	No
Isoniazid	Yes[e]	No	Yes[f]	Yes[f]
Itraconazole	Yes	No	No	No
Ketoconazole	Yes	No	No	No
Labetalol	Yes	No	No	No
Lamivudine	Yes	No	No	No
Leuprorelin	No	Yes	No	Yes
Levofloxacin	No	No	Yes	Yes
Lisinopril	Yes	No	No	No
Melphalan	Yes	No	No	No
Mercaptopurine	Yes	No	No	No
Methoxyflurane	No	Yes	No	Yes
Methyldopa	Yes	Yes	No	Yes
Mianserin	No	No	Yes	Yes
Moclobemide	No	Yes	No	No
Naproxen	Yes	Yes	Yes	Yes
Nefazodone	Yes	Yes	Yes	Yes
Nelfinavir	Yes	No	No	No
Nimesulide	No	No	Yes	Yes
Nitrofurantoin	Yes	Yes	No	Yes
Norfloxacin	No	Yes	No	Yes
Omeprazole	No	Yes	No	Yes
Orlistat	No	No	Yes	Yes
Oxyimino alkanoic acid derivative	Yes	No	No	No
Paracetamol (acetaminophen)	Yes	Yes	Yes	Yes
Paroxetine	Yes	Yes	No	No
Pemoline	Yes	No	No	No
Phenoxymethylpenicillin	No	Yes	No	Yes
Phenytoin	Yes	Yes	No	Yes
Piperacillin	No	Yes	No	Yes
Pivmecillinam	No	Yes	No	Yes

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Table V. Contd

Generic name	US	Sweden	Spain	Adjudicated/RUCAM case[a]
Propylthiouracil	Yes	No	No	No
Pyrazinamide	Yes[d]	No	Yes[g]	Yes[g]
Pyrimethamine-sulfadoxine	No	Yes	No	Yes
Quetiapine	Yes	No	No	No
Ranitidine	No	Yes	No	Yes
Rifampicin (rifampin)	Yes[d]	No	Yes[g]	Yes[g]
Rofecoxib	No	Yes	No	Yes
Sertraline	No	Yes	No	Yes
Simvastatin	Yes	Yes	Yes	Yes
Stavudine	Yes	No	No	No
Sulfasalazine	Yes	Yes	No	Yes
Tamoxifen	No	Yes	No	Yes
Terbinafine	Yes	No	No	No
Ticlopidine	No	Yes	No	Yes
Trimethoprim	Yes	No	No	No
Troglitazone	Yes	No	No	No
Valproic acid	Yes	Yes	No	Yes
Venlafaxine	Yes	No	No	No
Zafirlukast	Yes	No	No	No

a Adjudicated/RUCAM case indicates drugs identified as a cause of ALF using the standardized causality assessment tool, RUCAM.

b Including synthetic amfetamine (e.g. ecstasy [methylenedioxymethamfetamine]).

c In some cases, amoxicillin alone was implicated as a cause of acute liver failure.

d Only as combination with other anti-tuberculosis drugs.

e Either alone or in combination with other anti-tuberculosis drugs (e.g. rifampicin, pyrazinamide, ethambutol).

f Only as combination with other anti-tuberculosis drugs (e.g. rifampicin, pyrazinamide).

g Only as combination with other anti-tuberculosis drugs (e.g. as isoniazid/rifampicin, rifampicin/isoniazid/pyrazinamide).

RUCAM = Roussel Uclaf Causality Assessment Method.[4,5]

with a higher proportion of disproportionally-increased reporting frequency when compared with the absence of case reports or serious regulatory actions. Furthermore, EBGM scores are not in themselves absolute risk estimates and need to be interpreted as 'relative' values in light of reporting bias. For mature products, spontaneous reporting usually tapers in number, and the EBGM scores remain stable. For recently marketed drugs, a critical number of reports need to be in the database for EBGM scores to be robust. A sudden rise in EBGM scores may be an early indication of an adverse event signal; however, such a sudden rise must be viewed as hypothesis generating and viewed in the context of other pharmacovigilance tools. As discussed above, data interpretation requires caution and a broad knowledge of the system, clinical pharmacology, clinical science and potential biases. To assist such interpretation, we provided total number of reports and total number of cases (liver events) in addition to EBGM values.

Despite expert adjudication and a generally high standard of clinical care in all countries covered in this study, the regional differences in adjudicated drugs implicated in hepatotoxicity are notable. Some of the regional divergence may be attributed to regional variance in pharmaceutical policies (e.g. drug registration), prescribing practice (e.g. prescription volume, drug use and dosing, drug usage outside of licensed indications) and size of population covered by each study/registry (e.g. less use of amoxicillin/clavulanic acid and azithromycin in Sweden;

bentazepam, tetrabamate and ebrotidine only registered in Spain; flucloxacillin registered in Sweden, but not in the US or Spain; less use of chlorpromazine, doxycycline and telithromycin in Spain; clomethiazole mainly used in Europe; and nimesulide never approved in the US and Sweden). The observed regional divergence might also be attributed to differences in the time period and DILI cases captured (e.g. age and severity) in different studies (e.g. nefazodone was withdrawn in 2004, immediately after the DILIN was launched in the US). Some of the regional divergence seen with ibuprofen, fluvastatin, lovastatin and flutamide is, however, noteworthy. This could be explained by regional variation in concomitant medications/herbals/nutritional supplements, other dietary/environmental factors, genetics/ethnicity, sanitary systems, regulatory actions, media reports/publications or selective bias. Moreover, differences in the healthcare systems of these countries may have also influenced cases captured in different sites (e.g. number of cases, characteristics of patient population). Further analysis on regional divergence, taking into account drug availability, population sizes and prescription volume, will help us to clarify and understand the regional divergence observed in this study.

Although regional divergence was observed regarding paracetamol hepatotoxicity, this requires careful interpretation; paracetamol did not appear in the Swedish DILI study and DILIN study because DILI cases due to paracetamol were excluded from these studies. In Sweden, as in the US, paracetamol is the leading cause of ALF;[14,15] however, in Sweden, cases of paracetamol hepatotoxicity are usually reported to the Swedish Poisons Information Centre,[13] but not to the SADRAC, which was used in the previous Swedish studies and the present project. As previously reported, regional divergence does exist, in terms of paracetamol hepatotoxicity, between Spain vs US, England and Scandinavian countries, which can be explained by differences in cultural behaviour and drug regulation.[12,34] In Spain, paracetamol is not an over-the-counter drug. This limited accessibility may have contributed to the much lower frequency of paracetamol hepatotoxicity in Spain.[12,34]

Lastly, identifying potential hepatotoxins during drug development is a significant challenge. In fact, DILI is the primary adverse event that results in withdrawal of marketed drugs and curtails the development of innumerable promising compounds in pre-marketing studies.[35] At this point, our abilities to predict hepatotoxicity at a preclinical stage of drug development are limited. However, further analyses/characterization of the listed drugs linking the clinical information on degrees of their hepatotoxicity (i.e. frequency, severity) to the preclinical information on the drugs (e.g. chemical or physical properties, metabolism and biological effects) would eventually help us predict potential hepatotoxicity in an earlier phase of the drug development. For instance, some of the drugs identified in the adjudicated DILI cases showed, in the WHO database, stronger association with ALF rather than overall liver injury, while some drugs were associated with disproportionally increased reporting frequency of liver injury, but no reported cases of ALF. It is intriguing to see that several drugs more strongly associated with ALF have been shown to be related to mitochondrial toxicity and/or oxidative stress (paracetamol, disulfiram, flutamide, valproic acid and didanosine).[23] Further exploration is warranted on the potential link between clinical degrees of hepatotoxicity and preclinical drug characteristics.

Several limitations exist in this work in addition to the above-mentioned limitations associated with VigiBase™. First, we did not consider drug-drug interactions or other potential factors that could modify hepatotoxicity in the analysis. Since hepatotoxicity is likely influenced by various other factors (e.g. age, sex, ethnicity, foods, supplements and concomitant medications), the potential influence and magnitude of such factors should be evaluated in a different study setting. Second, herbs and dietary supplements were not assessed. Hepatoxicity due to such agents has been increasingly recognized; however, herbs and dietary supplements are less rigorously regulated than pharmaceuticals, and the quality, quantity and potential contaminants they contain vary significantly across preparations.[36] These factors presently limit the ability to analyse their

hepatotoxicity in the same rigorous manner as pharmaceuticals. Third, the paediatric population was not fully addressed in our study. Fourth, the information was collected only in Western countries. Global expansion of this DILI list should be considered in future. Lastly, our data do not yet assist in identifying the first DILI case associated with a novel drug. A high degree of clinical suspicion, along with careful exclusion of other causes of liver injury, remains essential.

Conclusions

In summary, this international collaborative work provides the most current, comprehensive list of drugs associated with liver injury in adjudicated or well vetted cases. Known hepatotoxicity is one of the essential elements in the RUCAM scoring methods; therefore, this list should assist clinicians in the clinical diagnosis of DILI by providing such information as a single resource. Furthermore, the information of reporting frequency in the WHO database provides a multifaceted 'weight of evidence' view of hepatotoxicity. To further increase application of this information in clinical practice and research, a web-based searching tool for the identified hepatotoxins (www.spanishdili.uma.es) has been developed to share the information compiled in this project. In conclusion, this paper provides a multifaceted assessment of drugs implicated in hepatotoxicity. We believe this information can facilitate the accurate clinical diagnosis of DILI and enhance research efforts to clarify the relationship of drugs to liver injury.

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