nature publishing group

See COMMENTARY page 784 and ARTICLE page 896

Case Definition and Phenotype Standardization in Drug-Induced Liver Injury

GP Aithal[1], PB Watkins[2], RJ Andrade[3,4], D Larrey[5], M Molokhia[6], H Takikawa[7], CM Hunt[8], RA Wilke[9], M Avigan[10], N Kaplowitz[11], E Bjornsson[12] and AK Daly[13]

Drug-induced liver injury (DILI) is the most frequent reason cited for the withdrawal of approved drugs from the market and accounts for up to 15% of the cases of acute liver failure. Investigators around the globe have begun to identify and study patients with DILI; several large registries and tissue banks are being established. In order to gain the maximum scientific benefit from these efforts, the definitions and terminology related to the clinical phenotypes of DILI must be harmonized. For this purpose, an international DILI Expert Working Group of clinicians and scientists reviewed current DILI terminology and diagnostic criteria so as to develop more uniform criteria that would define and characterize the spectrum of clinical syndromes that constitute DILI. Consensus was established with respect to the threshold criteria for definition of a case as being DILI, the pattern of liver injury, causality assessment, severity, and chronicity. Consensus was also reached on approaches to characterizing DILI in the setting of chronic liver diseases, including autoimmune hepatitis (AIH).

Idiosyncratic drug-induced liver injury (DILI) is best described as an adverse hepatic reaction that is unexpected on the basis of the pharmacological action of the drug administered. It is therefore distinct and different from DILI secondary to drug overdose. DILI, excluding injury caused by acetaminophen overdose, accounts for 7–15% of the cases of acute liver failure in Europe and the United States[1–4] and is the most frequent reason for the withdrawal of an approved drug from the market.[5] Estimates of the rate of incidence of DILI leading to hospital referral vary from 2.4 per 100,000 person-years (in a retrospective population-based study of 1.64 million UK subjects[6]) to 13.9 per 100,000 inhabitants (in a prospective analysis in France).[7] Complementary or alternative medicines are used by at least 20% of individuals in Western, Eastern, and African cultures,[8] and reports of DILI have increased.[9] Given its rarity, DILI may not be identified during clinical trials[10] and may come to light only after the culprit drug has obtained market approval and large numbers of patients have been exposed. In addition, in preregistration clinical trials, mild asymptomatic liver injuries, often characterized by asymptomatic elevations in liver enzymes, are commonly seen.[10] However, drugs capable of inducing severe DILI as well as drugs that have a low potential for causing severe injury (e.g., aspirin and heparin) can generate similar patterns of liver injury.[10] It is therefore necessary to develop an approach that can distinguish drugs that are likely to cause severe DILI from drugs that are unlikely to do so.

Furthermore, DILI is commonly misdiagnosed. An expert review of suspected DILI reports from primary and secondary care clinicians to the UK Committee on the Safety of Medicines revealed that approximately half of the cases were not DILI and that the misdiagnoses led to a delay in arriving at the correct diagnosis, possibly affecting patient care.[11] Inclusion of such cases in the characterization of the genetic architecture underlying DILI would introduce unnecessary misclassification and increase the likelihood of type II error. Therefore, clearly identified DILI criteria are needed to improve its accurate

[1]Nottingham Digestive Diseases Centre, National Institute for Health Research Biomedical Research Unit, Nottingham University Hospital National Health Service Trust, Nottingham, UK; [2]Hamner–University of North Carolina Institute for Drug Safety Sciences, University of North Carolina Hospitals, Research Triangle Park, North Carolina, USA; [3]Hepatology Unit, Hospital Universitario Virgen de la Victoria, Málaga, Spain; [4]Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Barcelona, Spain; [5]Service d'Hépato-Gastroenterologie et Transplantation, Hôpital Saint Eloi, Montpellier, France; [6]Department of Primary Care and Public Health Sciences, Division of Health and Social Care Research, King's College London, London, UK; [7]Department of Medicine, Teikyo University School of Medicine, Tokyo, Japan; [8]Clinical Safety Systems, GlaxoSmithKline, Research Triangle Park, North Carolina, USA; [9]Division of Clinical Pharmacology, Department of Medicine, Vanderbilt University, Nashville, Tennessee, USA; [10]Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland, USA; [11]USC Research Center for Liver Diseases, Keck School of Medicine, University of Southern California, Los Angeles, California, USA; [12]Division of Gastroenterology and Hepatology, Landspitali University Hospital, Reykjavik, Iceland; [13]Institute of Cellular Medicine, Newcastle University Medical School, Newcastle Upon Tyne, UK. Correspondence: GP Aithal (Guru.Aithal@nuh.nhs.uk)

Received 3 January 2011; accepted 2 March 2011; advance online publication 4 May 2011. doi:10.1038/clpt.2011.58

detection and assessment in genetic, clinical, and epidemiologic studies.

Advances in genetic research and molecular biology techniques have allowed researchers to begin to characterize the genetic components underlying some serious adverse drug reactions.[12] Genetic factors that increase susceptibility to clinically significant hepatotoxicity are increasingly being identified.[13–19] The identification and validation of these genetic markers will require a large and sufficiently diverse patient database as well as standardized phenotyping and genotyping. To meet this challenge, researchers around the world have begun to assemble cohorts of patients who have experienced DILI. Ongoing efforts to link comprehensive electronic medical records with archived biological material may accelerate the identification and recruitment of these rare patients.[20]

To harmonize these international efforts, and to facilitate cross-study comparisons and collaborations, it is important that the phenotypes of DILI be standardized and accepted. With this goal in mind, we sought to standardize the definitions, the optimal phenotyping data, and the process for causality assessment. This article presents the consensus statements generated from the discussions and meetings of an international expert working group (see the related Commentary in this issue of *Clinical Pharmacology & Therapeutics*). We have used the levels of evidence recommended by the Oxford Centre for Evidence-based Medicine because they are suitable for critical appraisal of the diagnosis, symptom prevalence, and natural history studies.[21]

DESCRIPTION OF PHENOTYPE

Clinical threshold for DILI

Liver injury in the context of DILI has been defined as an elevation in the serum concentration of alanine aminotransferase (ALT), conjugated bilirubin, or alkaline phosphatase exceeding 2× the upper limit of normal (ULN).[22] With the increasing incidence of nonalcoholic fatty liver disease, and the increased frequency with which liver tests are being performed as a part of routine investigations of nonspecific symptoms, modest ALT elevations are commonly detected.[23] Another relevant aspect is that small elevations in liver parameters, even if drug induced, may be transient in nature and may revert to baseline even when therapy is continued (as described with antituberculosis drug therapy and with statin therapy). These elevations may represent true mild liver injury with spontaneous resolution, or "adaptation," but they do not represent clinically important liver injury. A low threshold for the definition of DILI may therefore lead to unnecessary investigations and, on some occasions, an inappropriate withdrawal of otherwise useful medications. Raising the cutoff level of ALT elevation to 5× ULN is more likely to exclude clinically unimportant and self-limited drug-related events as well as nonalcoholic steatohepatitis not related to DILI. This has been supported by an observational study involving patients with atrial fibrillation (in whom underlying liver disease was excluded) over a 2-year period. A transient ALT concentration of ≥2× ULN affected 6–8%, whereas ALT concentration of ≥5× ULN was observed in 1.4% of the patients, with an incidence of 0.4/100 patient-years.[24] In clinical trials of more than 18,000 patients, predominantly female and without known liver disease at baseline, the prevalence of ALT concentration ≥5× ULN at baseline was 0.005%, and the incidence was 2.6/10,000 person-months (95% confidence interval 1.6–4.0).[25] An American Thoracic Society guidance recommends that subjects who have raised ALT levels between 2× ULN and 5× ULN but no symptoms should continue antituberculosis drug therapy, implying that elevations of ALT level below the recommended threshold (5× ULN) are unlikely to represent clinically significant DILI.[26] Therefore, it is the opinion of our Expert Working Group that an upper threshold of 5× ULN for ALT appears to better represent clinically important liver injury.

A majority of the hepatotoxicity networks have used alkaline phosphatase concentration ≥2× ULN as the threshold to identify the cholestatic pattern of liver injury;[22] the cases as defined by this criterion are associated with 5–14.3% mortality.[27,28] In addition, jaundiced patients with a hepatocellular pattern of liver injury are prone to acute liver failure (referred to as Hy's Law) and have a death or transplantation rate of ~10% (ref. 27). Therefore, we defined the clinical chemistry criteria for DILI as summarized in **Box 1**.

Clinical notes for clinical threshold for DILI

- The phenotype is not exclusive for any single hypothetical mechanism that may be responsible for DILI (e.g., chemically active drug metabolites, hypersensitivity reaction, and autoimmunity).
- These recommended thresholds can be reached at any point of the clinical event that is being considered (i.e., determined by the highest levels).
- If the patient has had previous liver injury and hence abnormal liver biochemistry prior to starting treatment with the implicated drug, ULN is replaced by the mean baseline values obtained prior to the exposure to the suspect drug, and the changes should be proportionate to this modified baseline (i.e., 5× baseline for ALT, 2× baseline for alkaline phosphatase, and 2× baseline for bilirubin with associated 3× baseline elevation in ALT).
- Aspartate transaminase levels may be used instead of ALT levels only when the latter are unavailable and when there

Box 1 Clinical chemistry criteria for drug-induced liver injury (DILI)

Any one of the following:

- More than or equal to fivefold elevation above the upper limit of normal (ULN) for alanine aminotransferase (ALT)
- More than or equal to twofold elevation above the ULN for alkaline phosphatase (ALP) (particularly with accompanying elevations in concentrations of 5′-nucleotidase or γ-glutamyl transpeptidase in the absence of known bone pathology driving the rise in ALP level)
- More than or equal to threefold elevation in ALT concentration and simultaneous elevation of bilirubin concentration exceeding 2× ULN

Level of evidence: 2b (exploratory/retrospective cohort studies)

is no known muscle pathology driving the rise in aspartate transaminase.
- Isolated hyperbilirubinemia is not DILI, even if it is associated with direct hyperbilirubinemia.
- Isolated elevation of γ-glutamyl transferase is insufficient to qualify as DILI.[29]
- These thresholds are not applicable to some types of chronic drug-associated liver injury (e.g., methotrexate-associated liver fibrosis and nodular regenerative hyperplasia).
- Some forms of liver injury, especially mitochondrial toxicity (e.g., valproate or fialuridine hepatotoxicity), may not induce these threshold values but may nevertheless cause clinically significant liver injury. These cases should be flagged on the basis of specific drug(s) and/or unique histological criteria, evaluated on an individual basis, and grouped separately as "other forms of DILI."

Defining the pattern of DILI

The most common clinical presentations of DILI are hepatocellular, cholestatic, and mixed, which should be defined on the basis of biochemical criteria (**Box 2**). The earliest identified pattern of liver injury should be recorded because the pattern of liver injury can change over time. Liver biopsy can confirm the biochemical classification and detect additional useful information for assigning causality, such as the presence of zonal injury or microvesicular steatosis; however, DILI histology is often nonspecific and can mimic other acute and chronic liver diseases.[8,30] Although liver biopsy is also useful in grading severity of injury, there is no standardized histological scoring system for DILI.[8,30]

Clinical notes for clinical pattern of DILI

- These descriptions of clinical patterns may not be applicable to insidious forms of DILI (e.g., methotrexate-associated liver fibrosis, tamoxifen-induced fatty liver disease, and nodular regenerative hyperplasia).
- Liver biopsy is not essential for the diagnosis of DILI but strengthens the diagnosis, particularly for cases in which an alternative diagnosis can be excluded only on the basis of findings from a liver biopsy.
- Liver biopsy can support the classification of a clinical pattern but does not replace classification based on biochemical criteria.

Box 2 Criteria for classifying the clinical pattern of drug-induced liver injury (DILI)

- Pattern of liver injury is based on earliest identified liver chemistry elevations that qualify as DILI (**Box 1**)
- Pattern of liver injury is defined using R value where R = (ALT/ULN)/(ALP/ULN). This will require estimation of alanine aminotransferase (ALT) (aspartate transaminase is used when ALT is unavailable) and alkaline phosphatase (ALP) from the same serum sample
- ALT activity = patient's ALT/upper limit of normal (ULN); ALP activity = patient's ALP/ULN; R = ALT activity/ALP activity
- Hepatocellular pattern of DILI = R ≥ 5
- Mixed pattern of DILI = R > 2 and < 5
- Cholestatic pattern of DILI = R ≤ 2
- Histological summary should be recorded separately (if liver biopsy has been performed). However, the liver biopsy interpretation will generally not replace the R value for purposes of classification

Level of evidence: 2b (retrospective cohort studies)

Grading the severity of DILI

The degree of elevation of enzyme levels alone may not reflect the severity of liver injury because these values do not accurately predict specific clinical outcomes. This is evident from the fact that none of the validated models of prognosis (such as Child–Pugh score, King's College Criteria for transplantation in acute liver failure, MELD and its modifications, and UKELD) includes liver enzymes as components. DILI accompanied by jaundice is associated with a 9–12% mortality in large, global DILI registries.[3,27] Without liver transplantation, such severe injury can progress to acute liver failure with likely mortality.[1,31] The criteria for defining acute liver failure have been well described and accepted in clinical practice. In classifying the severity of DILI, we have taken into account the evidence base, current definitions of acute liver failure, and the US Food and Drug Administration's Guidance for Industry on the premarketing assessment of DILI,[32] and we have aimed to achieve homogeneity in these recommendations. Our recommended classification of the clinical severity of DILI involves use of the highest measured values for each

Box 3 DILI severity index

Category	Severity	Description
1	Mild	Elevated alanine aminotransferase/alkaline phosphatase (ALT/ALP) concentration reaching criteria for DILI* but bilirubin concentration <2× upper limit of normal (ULN)
2	Moderate	Elevated ALT/ALP concentration reaching criteria for DILI* and bilirubin concentration ≥2× ULN, or symptomatic hepatitis
3	Severe	Elevated ALT/ALP concentration reaching criteria for DILI*, bilirubin concentration ≥2× ULN, and one of the following: • International normalized ratio ≥1.5 • Ascites[73] and/or encephalopathy, disease duration <26 weeks, and absence of underlying cirrhosis[31] • Other organ failure considered to be due to DILI
4	Fatal or transplantation	Death or transplantation due to DILI

*Criteria for DILI are defined in **Box 1**

Level of evidence: 1b (inception cohort studies)

Modified from ref. 70.

of the biochemical parameters during the course of DILI (**Box 3**).

In addition to the criteria in **Box 3**, hospitalization or prolongation of ongoing hospitalization should be noted because these would have socioeconomic consequences. However, hospitalization was not chosen as a distinct criterion for severity because indications for hospitalization vary substantially across the globe.

Clinical notes for severity of DILI

- Symptomatic hepatitis: symptoms attributed to hepatitis include fatigue, nausea, vomiting, right upper quadrant pain, itching, skin rash, jaundice, weakness, anorexia, and weight loss. Any of these symptoms, if attributed to DILI by the clinician responsible for the care of the patient, would qualify to be included under the severity assessment because these have been shown to be associated with a poorer clinical outcome.[33,34]
- Isolated coagulopathy in the absence of hyperbilirubinemia or encephalopathy is rare but theoretically possible. However, the clinical significance and impact of this on prognosis are unknown.

Causality assessment

Because there are no specific tests to confirm the diagnosis of DILI, causality assessment must be employed to establish a definitive link between drug intake and liver injury. The usual assessment tools for determining the causes of adverse events during drug therapy, as are used in many DILI cases reported to pharmacovigilance agencies, are inadequate in the evaluation of DILI. Although consensus opinion among hepatologists with expertise in DILI adjudication remains a "gold standard," this is impractical for widespread and international use. In contrast, the Roussel Uclaf Causality Assessment Method (RUCAM), endorsed by the Council of International Organizations of Medical Sciences,[35] and the DILI diagnostic scale[36] can be used by nonexperts and are clear improvements over instruments that are not specific to liver-related adverse events. When compared with the DILI diagnostic scale, the RUCAM scale was generally more reliable and correlated better with expert reviews.[37–39] The RUCAM data elements for hepatocellular or cholestatic/mixed liver injury are described in **Supplementary Tables S1** and **S2** online. However, the RUCAM has limitations when there are no data on drug re-challenge or de-challenge, when there is concomitant exposure to other drugs that are potentially hepatotoxic, when there are risk factors for DILI other than those listed in the algorithm, and when a drug typically produces delayed DILI (e.g., amoxicillin–clavulanate); also, the method does not fully eliminate subjectivity in the interpretation of data. Nonetheless, the RUCAM is the most commonly used diagnostic tool for DILI, and its formal and practical approach increases consistency and objectivity in causality assessment. Moreover, improved diagnostic instruments will most likely be based on modifications of the RUCAM; therefore, collecting causality assessment scores using the RUCAM may aid research in improving causality assessment. **Box 4** summarizes the recommended approach to causality assessment with respect to DILI. In the specific context of development and validation of a new tool of causality assessment (or a modified version of a current causality assessment method), it may be necessary to evaluate the performance of the new tool against the gold standard of the "expert assessment." The relative performance of the tool can be assessed in terms of sensitivity, specificity, and positive and negative predictive values.

Box 4 DILI causality assessment

- The Roussel Uclaf Causality Assessment Method (RUCAM) scale should be used for causality assessment (**Supplementary Tables S1 and S2** online)
- If more than one drug is suspected to be causing DILI, the RUCAM scale should be applied to each drug separately. If such assessments are not practical (e.g., antituberculosis medications), all the drugs involved may be implicated as a single entity
- If more than one drug is rated "possible" or higher by RUCAM, evaluation should be sought by a specialist to rank the drugs by order of likelihood of causing DILI. This may be done on the basis of the signature pattern of DILI and a review of the literature[74,75]

Level of evidence: 1b (validating cohort studies)

Clinical notes for causality assessment

- A temporal relationship needs to be established with respect to medication exposure, laboratory data, and relevant clinical signs and symptoms which may need to be extracted from free-text documents.[40]
- The "time of DILI onset" is the time of the first qualifying laboratory tests (see **Box 1**) except in cases in which symptoms directly related to DILI have clearly preceded the laboratory test that was performed.
- Under the category "course of the reaction," "decrease" in levels of liver enzymes is to be interpreted as a fall by at least 50% from the peak value above the ULN (one can thereafter evaluate time to decrease >50%).
- Risk factors: alcohol intake of >2 drinks per day (>14 units/week) in women and >3 drinks per day (>21 units/week) in men is considered the upper threshold for alcohol intake to be considered a risk factor.
- The dose (defined daily dose or cumulative dose) of a drug may be important to consider when assessing causality,[41] especially when considering the potential roles of more than one drug in a clinical episode. Although this does not appear in the RUCAM scale, information regarding the dose of the drug should be collected whenever possible because it may be used in the future with an improved diagnostic instrument. The possibility of a drug–drug interaction that modifies the drug concentration should also be taken into account: established drug–drug interactions should be highlighted, and possible drug–drug interactions (e.g., those with similar drug clearance pathways) can be noted.
- It should be specifically recorded whether the patient continued on the drug after the liver injury was identified and, if so, for what duration.

- Information regarding potential risk factors such as diabetes, metabolic syndrome,[42,43] sex, ethnicity, and body mass index should be collected whenever possible, although these are not currently considered in the RUCAM scale.
- Exclusions to reduce potential misclassification: information regarding hepatitis A, B, and C, cytomegalovirus, and Epstein–Barr virus serology[44] should be sought whenever possible. In addition, biliary obstruction, hypoxic injury, and other alternative causes of acute liver injury should be considered. There have been reports suggesting that infection with hepatitis E virus (HEV) may be misdiagnosed as DILI;[44] therefore, HEV testing should be carried out if available. Considering the high rate of false-positive tests of HEV immunoglobulin M antibody, HEV RNA should be considered the gold-standard test for acute HEV infection if the patient is in the icteric stage. However, detectability of HEV RNA appears to vary; it is detectable from 1 week before the icteric stage to 2 weeks during acute hepatitis, but in one study it was detectable in only 20% (4/22) of patients from 3 weeks to 3 months,[45] although detection of HEV RNA has been reported even up to 6 months.[46] HEV immunoglobulin M antibody is a useful assay because it is detectable for a period of a few months.[47] Additionally, the greater utility of HEV immunoglobulin M antibody screening as compared with HEV RNA screening was established in a large series of Japanese blood donors with elevated ALT levels[48] and in severe hepatitis in pregnant women in India.[49]
- In appropriate clinical settings, herpes simplex viral infection must be considered and excluded as a cause of prolonged cholestasis.
- When missing data limit causality assessment, expert assessment may be the only appropriate method to evaluate cases, and these should be grouped separately.

Chronicity

It has long been recognized that DILI can be associated with the development of progressive liver fibrosis and cirrhosis if treatment with the implicated drug is not discontinued.[50] More recently, persistence of DILI has been described after an acute episode of DILI, long after discontinuation of the implicated drug.[28,51–53] It is a challenge to distinguish persistence, which may simply reflect slow resolution of the initial injury, from a self-sustained and potentially progressive chronic liver injury.

Given that fibrosis can develop as soon as 3 months after acute DILI,[50] it has been suggested that liver injury can be considered chronic if it has persisted longer than 3 months.[54,55] In addition, natural history studies in large cohorts of subjects with acute liver injury of all etiologies indicate that liver failure develops within a 3-month period, which is associated with mortality.[56] A previous international consensus meeting recommended that a hepatocellular pattern of liver injury persisting >3 months after onset should be considered chronic liver injury.[22] Noting that cholestatic liver injury typically resolves more slowly than hepatocellular injury, it was proposed that >6 months be the criterion for defining cholestatic DILI. However, a recent prospective multicenter study of the natural history of DILI suggested that ~42% of those with an acute DILI episode had persistent elevation of liver enzymes at the 3-month follow-up, and 17% had persistent elevation at the 1-year follow-up.[57] Moreover, regardless of whether the injury was hepatocellular or cholestatic, the rate of resolution fell notably at 1 year, suggesting that this may be the best cutoff point to define chronicity.[57] We therefore propose that persistent DILI be defined as evidence of continued liver injury >3 months after hepatocellular or mixed liver injury, and >6 months after cholestatic liver injury, and that the term "chronic DILI" be reserved for cases in which there is evidence of persistent liver injury at >1 year after the onset of DILI (**Box 5**).

Clinical notes for chronicity of DILI

- Levels of liver enzyme elevations do not always reflect the degree of liver injury or its progression, and liver biopsy is clearly superior in this regard. But, in the context of assessing persistence or chronicity, measurement of liver enzymes may be the only practical method for identifying continued liver injury.
- The diagnosis of chronic DILI does not necessarily imply progressive liver injury because it appears that, in some patients, DILI will resolve after 1 year. This aspect requires further study. Progression of liver injury, in contrast to persistence of liver injury, can be established only if validated methods are used to demonstrate progression, such as clinical evidence of development or progression of cirrhosis, evidence of development or progression as shown by liver biopsy or other emerging tools such as ultrasound elastography, and serum markers of fibrosis.

Acute DILI occurring in patients with chronic liver disease. Patients with chronic liver disease such as chronic viral hepatitis can have acute episodes of DILI that may be difficult to distinguish

Box 5 Characteristics of persistent and chronic drug-induced liver injury (DILI)

- Initial clinical episode met the criteria to qualify as acute DILI (**Box 1**)
- Initial episode on causality assessment has been considered possible, probable, or highly probable DILI on the basis of Roussel Uclaf Causality Assessment Method scoring criteria. Persistent DILI is defined as evidence of continued liver injury after withdrawal of the causative agent, beyond 3 months of follow-up for hepatocellular and mixed DILI, and beyond 6 months for cholestatic DILI
- Chronic DILI is defined as evidence of continued liver injury after withdrawal of the causative agent beyond 12 months of follow-up, regardless of the classification of DILI
- There is no new risk factor other than exposure to the suspect drug that would explain the persistence of liver injury, and other causes of chronic liver diseases have been excluded

Level of evidence: 4 (prognostic cohort studies of modest quality)

from the natural history of their underlying disease. In these cases, standard causality assessment procedures can usually be applied, but additional phenotypic information, such as viral titers in patients with chronic viral hepatitis or CD4 counts in patients with AIDS, may be important.

Drug-associated chronic liver diseases. In contrast to acute DILI, treatment with some drugs has been associated with a variety of chronic liver diseases, including fatty liver disease, fibrosis, cirrhosis, nodular regenerative hyperplasia, and vascular diseases. Some drugs may aggravate or even initiate these conditions. For example, tamoxifen has been shown to be associated with fatty liver disease in those who have preexisting metabolic syndrome.[43] Standard causality assessment methods do not work well in these conditions, given the prolonged induction time to the recognition of chronic liver disease and other risk factors acting in conjunction with the drug as component causes.[42,43] Patients with suspected chronic liver disease due to, or aggravated by, a drug will be classified according to whether chronic liver disease was present before starting the implicated drug (**Box 6**). A liver biopsy can provide critical information in chronic hepatitis with respect to the assessment of disease etiology, inflammation, and fibrosis or cirrhosis.[58]

Clinical notes for drug-associated chronic liver disease

- The usual causality assessment methods, including the RUCAM scale, are not suitable for use in the context of drug-associated chronic liver diseases. In the latter, causality can be determined by adopting an accepted method of ranking levels of evidence and carrying out a critical, formal appraisal of the likelihood of a particular drug being a potential risk factor for the relevant form of chronic liver disease.
- Validated markers of chronic liver disease may include emerging tools such as ultrasound elastography and serum markers of fibrosis, in the appropriate context.[59,60] This information should be included if available.

Drug-induced autoimmune hepatitis. DILI caused by certain drugs, including minocycline, α-methyldopa, nitrofurantoin, indomethacin, and diclofenac, can mimic idiopathic true autoimmune hepatitis (AIH).[61,62] In addition, given that AIH is believed to have environmental triggers, it is at least theoretically possible that a drug could initiate *de novo* AIH. Furthermore, medications such as tumor necrosis factor-α inhibitors may unmask or aggravate preexisting AIH.[63,64] The situation is further confounded because patients genetically predisposed to DILI associated with the use of certain drugs may also be predisposed to develop AIH.[16] It can be challenging to distinguish between drug-induced autoimmune features, *de novo* AIH initiated or unmasked by a drug, and a flare-up of AIH unrelated to drug therapy. A recently developed abbreviated scoring system for the diagnosis of AIH[65] has been validated in independent cohorts and should be used to support the diagnosis of all three conditions; however, it does not distinguish among them. The scoring system requires assessment of multiple autoantibodies (antinuclear antibody, smooth muscle cell antibody, liver–kidney microsomal antibodies, and soluble liver/liver–pancreas antibodies); quantitative serum γ-globulins; exclusion of viral hepatitis; and, ideally, histological evaluation of the liver.[66,67] In >80% of patients with idiopathic AIH, there is a relapse within 1 year in the absence of adequate immunosuppression, whereas in patients with drug-induced AIH, there is no relapse.[61,68,69] This feature is probably the most reliable one to use in identifying drug-induced AIH (**Box 7**);[61] however, the appropriate duration of therapy with immunosuppressant agents in this setting is still unknown.

Algorithm for consideration, diagnosis, and classification of DILI

Figure 1 presents an algorithm that was generated on the basis of the recommendations for the diagnosis and classification of DILI.

Optimal data to be collected

For genetic studies, DILI cases may be derived from a variety of sources. We recommend the collection of the patient history data described in **Table 1**.

Box 6 Characteristics of drug-associated chronic liver disease

- Evidence of chronic liver disease is established on the basis of validated methods such as clinical evidence of cirrhosis, histological evidence of chronic liver disease, and imaging in cases of vascular disorder and tumors, as appropriate
- Evidence of drug intake for an appropriate duration preceding the appearance of symptoms, signs, or test results suggestive of chronic liver disease
- Exclusion of other etiologies of chronic disease (outlined in **Supplementary Table S3** online)

Level of evidence: 1b (prospective/validating cohort studies with good follow-up)

Box 7 Characteristics of drug-induced autoimmune hepatitis (AIH)

- The score is ≥6 points on simplified diagnostic criteria for AIH (scores >6 points with the simplified criteria can be obtained if liver biopsy is performed. Hennes *et al.*[65] consider a probable diagnostic score to be ≥6)
- Injury resolves on withdrawal of medication that triggered the AIH, with or without immunosuppressive therapy to induce remission
- No relapse within a period of 1 year after withdrawal of all immunosuppressants. This criterion needs further confirmation and cannot be considered pathognomonic because it is quite variable depending on the cohorts analyzed

Level of evidence: 2b (exploratory cohort study)

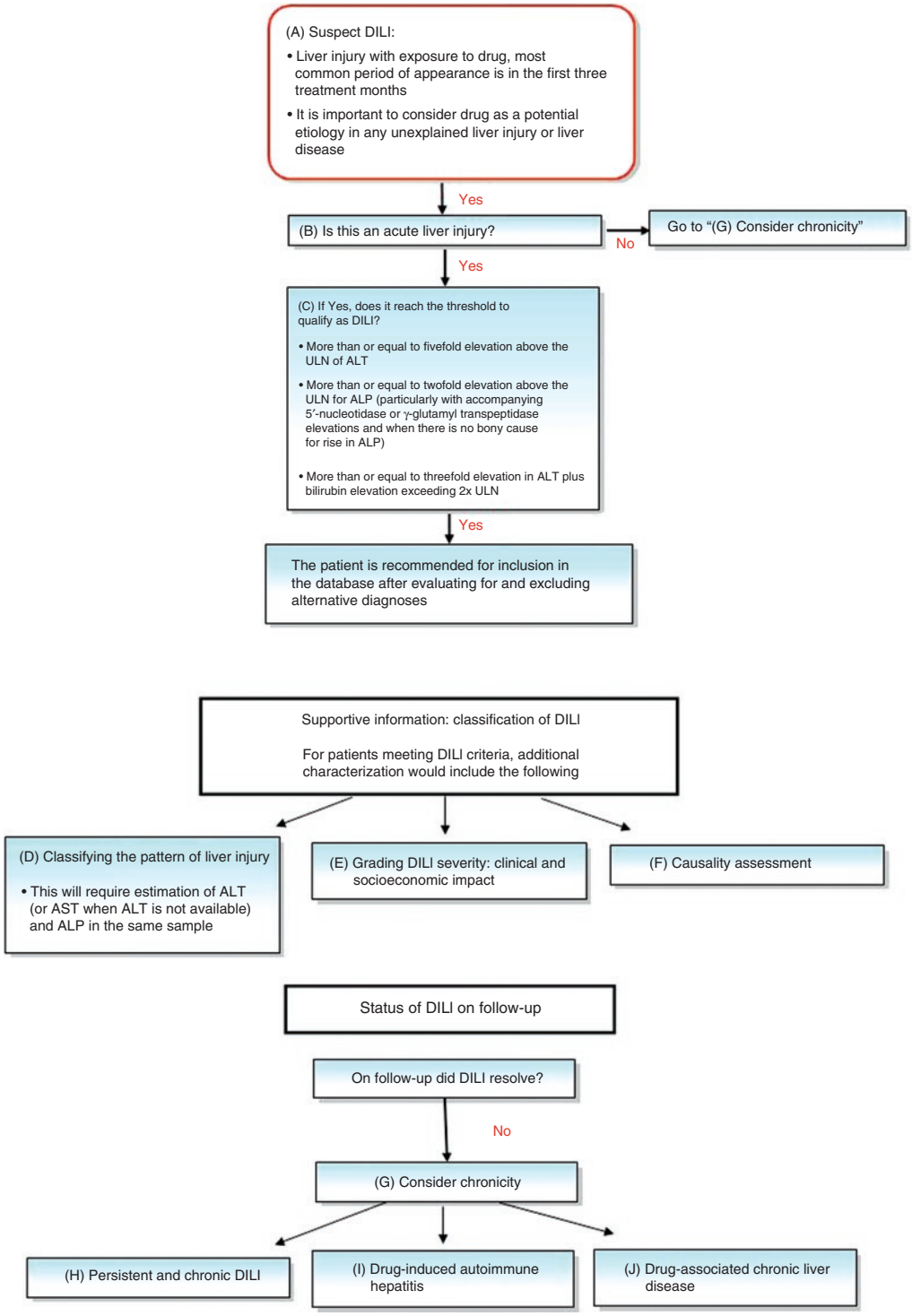

Figure 1 Algorithm for consideration, diagnosis, and classification of drug-induced liver injury (DILI). ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate transaminase; ULN, upper limit of normal.

CONSENSUS PROCESS

Phenotypic standardization project

In response to a need for large patient databases for genetic analyses, the International Serious Adverse Event Consortium, a nonprofit group of industrial, academic, and regulatory entities created for the purpose of researching the genetic basis of serious adverse events, initiated the Phenotype Standardization Project in collaboration with The Wellcome Trust in the United Kingdom and the US Food and Drug Administration. After several teleconferences and a meeting of the expert working group (October 2009), the consortium organized a consensus conference at the Wellcome Trust Hinxton Campus (Hinxton, England) on 16 March 2010. The DILI consensus group included 17 delegates representing hepatologists, gastroenterologists,

Table 1 Patient history data collection for DILI cases

Case identifier
Demographics: age, gender, country of birth, ethnicity, height, weight
Country of birth
Parents' ethnicity
Suspect drug, daily dose
Start/stop dates, including re-initiation or re-challenge, and duration of drug exposure
Concomitant drugs including over-the-counter and alternative medications with dates started/stopped
Underlying medical conditions including presence of ischemia/hypotension, severe hypoxemia or congestive heart failure, sepsis, or pregnancy coincident with onset of liver chemistry elevations
Clinical signs: fever, rash, jaundice, encephalopathy
Date of symptom onset
Symptoms: fatigue, weakness, nausea, anorexia, abdominal pain, dark urine, pruritus
History of alcohol intake: amount in average drinks/day (units per week) and duration in years
Previous liver disease or metabolic syndrome (obesity, insulin resistance, diabetes, hypertension, dyslipidemia)
Extrahepatic features: presence of hypersensitivity features such as rash, eosinophilia, lymphopenia, positive titers of autoantibodies (listed below)
Laboratory evaluation
Liver biochemistry longitudinally: alanine aminotransferase, aspartate transaminase, bilirubin (with fractionation, if available), alkaline phosphatase, including values before drug exposure if available, peak values with dates, time to normalization (if liver biochemistry has not normalized, then values at 3 months for hepatocellular or 6 months for cholestatic/mixed and until resolution, with long-term follow-up, if possible)
Hematologic/coagulation: eosinophilia, lymphopenia, international normalized ratio
Viral hepatitis serology: hepatitis A immunoglobulin M (IgM) antibody[a], hepatitis B surface antigen, hepatitis B core antibody, hepatitis C RNA[a], hepatitis E IgM antibody[a], hepatitis E RNA (if available)[a], Epstein–Barr viral capsid antigen IgM antibody[a], cytomegalovirus IgM antibody[a]
Autoimmune serology: total serum immunoglobulin G, anti-nuclear antibody, anti–smooth muscle antibody, anti–liver–kidney microsomal antibody type 1, or soluble liver/liver–pancreas antibody
Any additional tests performed to exclude clinically relevant differential diagnosis (e.g., CD4 count to exclude immune reconstitution in AIDS patients with chronic viral hepatitis)
Liver imaging results (abdominal ultrasound abdomen, computerized tomography, magnetic resonance imaging, or other liver imaging), as appropriate
Liver biopsy results, if available

[a]Repeat with convalescent serum if positive.

clinical pharmacologists, epidemiologists, electronic medical database managers, regulatory agencies, and journal and industry representatives.

The goal of each Expert Working Group within the consortium was to identify the phenotypic requirements that would allow accurate identification of patients with a given serious adverse drug reaction and to develop rigorously defined phenotypic algorithms to assist in the identification and recruitment of such cases for a collaborative database. In addition, recommendations were made about the types of data/samples to be collected for each patient.

DILI working group

Initially, a comprehensive literature review was conducted to assess current terminology and diagnostic criteria for DILI. Next, the working group agreed on what aspects of DILI needed to be addressed. These predetermined aspects of DILI were discussed (in a meeting of the working group in October 2009 and a teleconference in December 2009). The first draft of agreed criteria was presented at the Phenotype Standardization Project conference (March 2010), and the delegates discussed all the material presented. After the session, the second draft of the consensus statement was prepared on the basis of the decisions made during the meeting. Subsequent drafts were read and annotated by all the delegates, and these drafts were iteratively re-edited until the final consensus was reached. The final recommendations are collated herein.

The aim of the recommendations from the DILI Expert Working Group is to achieve consistency, homogeneity, and objectivity whenever possible in the definition, characterization, and classification of the full spectrum of clinical syndromes that constitute drug-induced hepatotoxicity. These recommendations included the following components: (i) DILI case definition threshold criteria, (ii) pattern of liver injury, (iii) causality assessment, (iv) severity assessment, (v) chronicity, and (vi) an algorithm for evaluation of potential subjects. In addition, recommendations were made about the types of data/samples to be collected from each patient with DILI for the purpose of organizing and directing follow-up studies.

Methodological considerations

The DILI working group formed their consensus statement within the following framework: phenotypic definitions were required to be useful for identifying clinically important cases prospectively within the context of routine clinic practice and/or retrospectively from randomized trials and existing databases and for minimizing DILI misclassification arising from other causes. The issue of phenotyping of controls was not addressed.

The consensus is built on previous recommendations and publications. These included the definitions and criteria developed by an international working group of hepatologists and scientists under the auspices of the Council for International Organizations of Medical Sciences.[35] These recommendations have formed the basis of case definitions for several DILI publications and have been adopted by hepatotoxicity networks.[27,38] The development of prospective registries of DILI cases and cross-institutional research networks, especially the Drug Induced Liver Injury Network in the United States,[70] has contributed to further refinement in the terminologies used to characterize DILI. In 2008, the National Institutes of Health, the National Library of Medicine, and the National Institute of Diabetes and Digestive and Kidney Diseases hosted a workshop, "Drug-Induced Liver Injury: Standardization of Nomenclature

and Causality Assessment," the summary of which has been published[71] along with the minimal criteria for defining DILI.[72] Recently, the Food and Drug Administration issued a guidance for industry on the premarketing evaluation of DILI, using information gathered during clinical trials, in an effort to enhance patient safety and better assess each drug's potential to cause severe liver injury. These guidelines describe the agency's current suggestions and recommendations regarding DILI.[32]

CONCLUSION

Consistent case definition and phenotypic characterization are of paramount importance in investigations designed to identify the genetic and environmental determinants of DILI susceptibility, particularly across multinational studies. We have developed a consensus among an international group of investigators and experts concerning definitions of DILI phenotypes and recommendations regarding essential clinical data and data from laboratory tests and imaging. These recommendations should facilitate cross-study comparisons and collaboration among researchers in the field.

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at http://www.nature.com/cpt

ACKNOWLEDGMENTS

We are grateful for the interest and contributions of the following people who participated in the DILI section of the consensus conference: Peter Arlett, MD (European Medicines Agency), Fiona Godlee, MD (BMJ Group), CE Eapen, MD (Christian Medical College, Vellore, India), Catherine King (Medicines & Healthcare Products Regulatory Agency), Saad Shakir, MD (Drug Safety Research Unit), Howard Snow, MD (Novartis Pharmaceuticals), and Ashraf Youssef, MD (Takeda Global Research & Development). We also thank Maribel Lucena (University of Málaga, Spain) for her helpful comments on the manuscript. We acknowledge the comments received from the members of the Hepatotoxicity Special Interest Group of the American Association for the Study of Liver Diseases; these comments were considered in the preparation of this article.

CONFLICT OF INTEREST

This initiative was supported by the International Serious Adverse Event Consortium (iSAEC) in collaboration with the US Food and Drug Administration (FDA) and The Wellcome Trust. G.P.A., R.J.A., D.L., M.M., E.B., and A.D. are investigators in the International Drug-Induced Liver Injury Consortium (iDILIC), which is supported by the iSAEC. M.M. has received grants from the SAEC consortium and from AstraZeneca and Pfizer. P.B.W. has consulting contracts with Actelion, Alnara, BMS, Cempra, Esai, Furiex, Genzyme, GlaxoSmithKline, Gilead, Hoffmann–LaRoche, Idenix, Johnson & Johnson, TEVA, Merck, Novartis, Nuon, Orixigen, Pfizer, Sanofi-Aventis, Takeda, Wyeth, Sepracor, Schering-Plough, Genzyme, Elan, and Enanta but holds no stock in and has received no research support from these or other companies in the pharmaceutical industry. N.K. has consulting contracts with GlaxoSmithKline, Roche, TEVA, Merck, Novartis, BMS, Johnson & Johnson, Hepregen Biotech, Eisai, Karo-Bio, Wyeth, Dailchi Sankyo, Sanofi-Aventis, Pfizer, ISIS, Idenix, Sepracor, Schering-Plough, Genzyme, Elan, and Enanta but holds no stock in and has received no research support from these or other companies in the pharmaceutical industry. C.M.H. is a full-time employee of GlaxoSmithKline. The other authors (R.A.W., H.T., and M.A.) declared no conflicts of interest.

The views expressed in this publication are solely those of the authors and not necessarily of the US FDA.

1. Ostapowicz, G. *et al*. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. *Ann. Intern. Med.* **137**, 947–954 (2002).
2. O'Grady, J.G. Acute liver failure. *Postgrad. Med. J.* **81**, 148–154 (2005).
3. Björnsson, E., Jerlstad, P., Bergqvist, A. & Olsson, R. Fulminant drug-induced hepatic failure leading to death or liver transplantation in Sweden. *Scand. J. Gastroenterol.* **40**, 1095–1101 (2005).
4. Russo, M.W., Galanko, J.A., Shrestha, R., Fried, M.W. & Watkins, P. Liver transplantation for acute liver failure from drug induced liver injury in the United States. *Liver Transpl.* **10**, 1018–1023 (2004).
5. Navarro, V.J. & Senior, J.R. Drug-related hepatotoxicity. *N. Engl. J. Med.* **354**, 731–739 (2006).
6. de Abajo, F.J., Montero, D., Madurga, M. & García Rodríguez, L.A. Acute and clinically relevant drug-induced liver injury: a population based case-control study. *Br. J. Clin. Pharmacol.* **58**, 71–80 (2004).
7. Sgro, C. *et al*. Incidence of drug-induced hepatic injuries: a French population-based study. *Hepatology* **36**, 451–455 (2002).
8. Ramachandran, R. & Kakar, S. Histological patterns in drug-induced liver disease. *J. Clin. Pathol.* **62**, 481–492 (2009).
9. Frazier, T.H. & Krueger, K.J. Hepatotoxic herbs: will injury mechanisms guide treatment strategies? *Curr. Gastroenterol. Rep.* **11**, 317–324 (2009).
10. Watkins, P.B., Seligman, P.J., Pears, J.S., Avigan, M.I. & Senior, J.R. Using controlled clinical trials to learn more about acute drug-induced liver injury. *Hepatology* **48**, 1680–1689 (2008).
11. Aithal, G.P., Rawlins, M.D. & Day, C.P. Accuracy of hepatic adverse drug reaction reporting in one English health region. *BMJ* **319**, 1541 (1999).
12. Pirmohamed, M. Pharmacogenetics of idiosyncratic adverse drug reactions. *Handb. Exp. Pharmacol.* 477–491 (2010).
13. Aithal, G.P. *et al*. Hepatic adducts, circulating antibodies, and cytokine polymorphisms in patients with diclofenac hepatotoxicity. *Hepatology* **39**, 1430–1440 (2004).
14. Daly, A.K., Aithal, G.P., Leathart, J.B., Swainsbury, R.A., Dang, T.S. & Day, C.P. Genetic susceptibility to diclofenac-induced hepatotoxicity: contribution of UGT2B7, CYP2C8, and ABCC2 genotypes. *Gastroenterology* **132**, 272–281 (2007).
15. Daly, A.K. *et al*. HLA-B*5701 genotype is a major determinant of drug-induced liver injury due to flucloxacillin. *Nat. Genet.* **41**, 816–819 (2009).
16. Kindmark, A. *et al*. Genome-wide pharmacogenetic investigation of a hepatic adverse event without clinical signs of immunopathology suggests an underlying immune pathogenesis. *Pharmacogenomics J.* **8**, 186–195 (2008).
17. Aithal, G.P. & Daly, A.K. Preempting and preventing drug-induced liver injury. *Nat. Genet.* **42**, 650–651 (2010).
18. Donaldson, P.T. *et al*. Human leucocyte antigen class II genotype in susceptibility and resistance to co-amoxiclav-induced liver injury. *J. Hepatol.* **53**, 1049–1053 (2010).
19. Singer, J.B. *et al*. A genome-wide study identifies HLA alleles associated with lumiracoxib-related liver injury. *Nat. Genet.* **42**, 711–714 (2010).
20. Wilke, R.A. *et al*. The emerging role of electronic medical records in pharmacogenomics. *Clin. Pharmacol. Ther.* **89**, 379–386 (2011).
21. Centre for Evidence Based Medicine. Levels of evidence <http://www.cebm.net/?o=1025> (March 2009).
22. Bénichou, C. Criteria of drug-induced liver disorders. Report of an international consensus meeting. *J. Hepatol.* **11**, 272–276 (1990).
23. Neuschwander-Tetri, B.A. & Caldwell, S.H. Nonalcoholic steatohepatitis: summary of an AASLD Single Topic Conference. *Hepatology* **37**, 1202–1219 (2003).
24. Makar, G.A. *et al*. Incidence and prevalence of abnormal liver associated enzymes in patients with atrial fibrillation in a routine clinical care population. *Pharmacoepidemiol. Drug Saf.* **17**, 43–51 (2008).
25. Weil, J.G., Bains, C., Linke, A., Clark, D.W., Stirnadel, H.A. & Hunt, C.M. Background incidence of liver chemistry abnormalities in a clinical trial population without underlying liver disease. *Regul. Toxicol. Pharmacol.* **52**, 85–88 (2008).
26. Saukkonen, J.J. *et al*. An official ATS statement: hepatotoxicity of antituberculosis therapy. *Am. J. Respir. Crit. Care Med.* **174**, 935–952 (2006).
27. Andrade, R.J. *et al*. Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish registry over a 10-year period. *Gastroenterology* **129**, 512–521 (2005).
28. Chalasani, N. *et al*. Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. *Gastroenterology* **135**, 1924–34, 1934.e1 (2008).
29. Dufour, D.R., Lott, J.A., Nolte, F.S., Gretch, D.R., Koff, R.S. & Seeff, L.B. Diagnosis and monitoring of hepatic injury. I. Performance characteristics of laboratory tests. *Clin. Chem.* **46**, 2027–2049 (2000).

30. Kleiner, D.E. The pathology of drug-induced liver injury. *Semin. Liver Dis.* **29**, 364–372 (2009).
31. Polson, J. & Lee, W.M. AASLD position paper: the management of acute liver failure. *Hepatology* **41**, 1179–1197 (2005).
32. US Food and Drug Administration. Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Guidance for Industry: Drug-Induced Liver Injury—Premarketing Clinical Evaluation (2009).
33. Agal, S. *et al*. Monitoring and management of antituberculosis drug induced hepatotoxicity. *J. Gastroenterol. Hepatol.* **20**, 1745–1752 (2005).
34. Lobato, M.N., Reves, R.R., Jasmer, R.M., Grabau, J.C., Bock, N.N. & Shang, N. Adverse events and treatment completion for latent tuberculosis in jail inmates and homeless persons. *Chest* **127**, 1296–1303 (2005).
35. Danan, G. & Benichou, C. Causality assessment of adverse reactions to drugs–I. A novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries. *J. Clin. Epidemiol.* **46**, 1323–1330 (1993).
36. Maria, V.A. & Victorino, R.M. Development and validation of a clinical scale for the diagnosis of drug-induced hepatitis. *Hepatology* **26**, 664–669 (1997).
37. Aithal, G.P., Rawlins, M.D. & Day, C.P. Clinical diagnostic scale: a useful tool in the evaluation of suspected hepatotoxic adverse drug reactions. *J. Hepatol.* **33**, 949–952 (2000).
38. Lucena, M.I., Camargo, R., Andrade, R.J., Perez-Sanchez, C.J. & Sanchez De La Cuesta, F. Comparison of two clinical scales for causality assessment in hepatotoxicity. *Hepatology* **33**, 123–130 (2001).
39. Rockey, D.C. *et al*. Causality assessment in drug-induced liver injury using a structured expert opinion process: comparison to the Roussel-Uclaf causality assessment method. *Hepatology* **51**, 2117–2126 (2010).
40. Xu, H., Stenner, S.P., Doan, S., Johnson, K.B., Waitman, L.R. & Denny, J.C. MedEx: a medication information extraction system for clinical narratives. *J. Am. Med. Inform. Assoc.* **17**, 19–24 (2010).
41. Lammert, C., Einarsson, S., Saha, C., Niklasson, A., Bjornsson, E. & Chalasani, N. Relationship between daily dose of oral medications and idiosyncratic drug-induced liver injury: search for signals. *Hepatology* **47**, 2003–2009 (2008).
42. Rosenberg, P. *et al*. Psoriasis patients with diabetes type 2 are at high risk of developing liver fibrosis during methotrexate treatment. *J. Hepatol.* **46**, 1111–1118 (2007).
43. Bruno, S. *et al*. Incidence and risk factors for non-alcoholic steatohepatitis: prospective study of 5408 women enrolled in Italian tamoxifen chemoprevention trial. *BMJ* **330**, 932 (2005).
44. Dalton, H.R. *et al*. The role of hepatitis E virus testing in drug-induced liver injury. *Aliment. Pharmacol. Ther.* **26**, 1429–1435 (2007).
45. Nanda, S.K., Ansari, I.H., Acharya, S.K., Jameel, S. & Panda, S.K. Protracted viremia during acute sporadic hepatitis E virus infection. *Gastroenterology* **108**, 225–230 (1995).
46. Tamura, A. *et al*. Persistent infection of hepatitis E virus transmitted by blood transfusion in a patient with T-cell lymphoma. *Hepatol. Res.* **37**, 113–120 (2007).
47. Aggarwal, R. & Krawczynski, K. Hepatitis E: an overview and recent advances in clinical and laboratory research. *J. Gastroenterol. Hepatol.* **15**, 9–20 (2000).
48. Fukuda, S. *et al*. Unchanged high prevalence of antibodies to hepatitis E virus (HEV) and HEV RNA among blood donors with an elevated alanine aminotransferase level in Japan during 1991-2006. *Arch. Virol.* **152**, 1623–1635 (2007).
49. Patra, S., Kumar, A., Trivedi, S.S., Puri, M. & Sarin, S.K. Maternal and fetal outcomes in pregnant women with acute hepatitis E virus infection. *Ann. Intern. Med.* **147**, 28–33 (2007).
50. Maddrey, W.C. & Boitnott, J.K. Drug-induced chronic liver disease. *Gastroenterology* **72**, 1348–1353 (1977).
51. Aithal, P.G. & Day, C.P. The natural history of histologically proved drug induced liver disease. *Gut* **44**, 731–735 (1999).
52. Andrade, R.J. *et al*. Outcome of acute idiosyncratic drug-induced liver injury: long-term follow-up in a hepatotoxicity registry. *Hepatology* **44**, 1581–1588 (2006).
53. Björnsson, E., Kalaitzakis, E., Av Klinteberg, V., Alem, N. & Olsson, R. Long-term follow-up of patients with mild to moderate drug-induced liver injury. *Aliment. Pharmacol. Ther.* **26**, 79–85 (2007).
54. Seeff, L.B. Drug-induced chronic liver disease, with emphasis on chronic active hepatitis. *Semin. Liver Dis.* **1**, 104–115 (1981).
55. Farrell, G.C. *Drug-Induced Liver Disease* (Churchill Livingston, Edinburgh, UK, 1994).
56. O'Grady, J.G., Schalm, S.W. & Williams, R. Acute liver failure: redefining the syndromes. *Lancet* **342**, 273–275 (1993).
57. Borraz, Y. *et al*. Would it be desirable to modify the cut-off point for definition of chronicity in drug-induced liver injury (DILI)? (abstract). *Hepatology* **52**, 457A (2010).
58. Desmet, V.J., Gerber, M., Hoofnagle, J.H., Manns, M. & Scheuer, P.J. Classification of chronic hepatitis: diagnosis, grading and staging. *Hepatology* **19**, 1513–1520 (1994).
59. Laharie, D. *et al*. Assessment of liver fibrosis with transient elastography and FibroTest in patients treated with methotrexate for chronic inflammatory diseases: a case-control study. *J. Hepatol.* **53**, 1035–1040 (2010).
60. Berends, M.A. *et al*. Biochemical and biophysical assessment of MTX-induced liver fibrosis in psoriasis patients: Fibrotest predicts the presence and Fibroscan predicts the absence of significant liver fibrosis. *Liver Int.* **27**, 639–645 (2007).
61. Björnsson, E. *et al*. Drug-induced autoimmune hepatitis: clinical characteristics and prognosis. *Hepatology* **51**, 2040–2048 (2010).
62. Aithal, G.P. & Day, C.P. Nonsteroidal anti-inflammatory drug-induced hepatotoxicity. *Clin. Liver Dis.* **11**, 563–75, vi (2007).
63. Sokolove, J. *et al*. Risk of elevated liver enzymes associated with TNF inhibitor utilisation in patients with rheumatoid arthritis. *Ann. Rheum. Dis.* **69**, 1612–1617 (2010).
64. Mancini, S., Amorotti, E., Vecchio, S., Ponz de Leon, M. & Roncucci, L. Infliximab-related hepatitis: discussion of a case and review of the literature. *Intern. Emerg. Med.* **5**, 193–200 (2010).
65. Hennes, E.M. *et al*. Simplified criteria for the diagnosis of autoimmune hepatitis. *Hepatology* **48**, 169–176 (2008).
66. Czaja, A.J. Performance parameters of the diagnostic scoring systems for autoimmune hepatitis. *Hepatology* **48**, 1540–1548 (2008).
67. Neuhauser, M. *et al*. Autoimmune hepatitis-PBC overlap syndrome: a simplified scoring system may assist in the diagnosis. *Am. J. Gastroenterol.* **105**, 345–353 (2010).
68. Hegarty, J.E., Nouri Aria, K.T., Portmann, B., Eddleston, A.L. & Williams, R. Relapse following treatment withdrawal in patients with autoimmune chronic active hepatitis. *Hepatology* **3**, 685–689 (1983).
69. Johnson, P.J., McFarlane, I.G. & Williams, R. Azathioprine for long-term maintenance of remission in autoimmune hepatitis. *N. Engl. J. Med.* **333**, 958–963 (1995).
70. Fontana, R.J. *et al*. Drug-Induced Liver Injury Network (DILIN) prospective study: rationale, design and conduct. *Drug Saf.* **32**, 55–68 (2009).
71. Fontana, R.J. *et al*. Standardization of nomenclature and causality assessment in drug-induced liver injury: summary of a clinical research workshop. *Hepatology* **52**, 730–742 (2010).
72. Agarwal, V.K., McHutchison, J.G. & Hoofnagle, J.H. Important elements for the diagnosis of drug-induced liver injury. *Clin. Gastroenterol. Hepatol.* **8**, 463–470 (2010).
73. Brinker, A.D. *et al*. Telithromycin-associated hepatotoxicity: clinical spectrum and causality assessment of 42 cases. *Hepatology* **49**, 250–257 (2009).
74. Suzuki, A. *et al*. Drugs associated with hepatotoxicity and their reporting frequency of liver adverse events in VigiBase: unified list based on international collaborative work. *Drug Saf.* **33**, 503–522 (2010).
75. Biour, M., Ben Salem, C., Chazouillères, O., Grangé, J.D., Serfaty, L. & Poupon, R. [Drug-induced liver injury; fourteenth updated edition of the bibliographic database of liver injuries and related drugs]. *Gastroenterol. Clin. Biol.* **28**, 720–759 (2004).