World Journal of Hepatology

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.4254/wjh.v6.i1.17

World J Hepatol 2014 January 27; 6(1): 17-32
ISSN 1948-5182 (online)

REVIEW

Drug and herb induced liver injury: Council for International Organizations of Medical Sciences scale for causality assessment

Rolf Teschke, Albrecht Wolff, Christian Frenzel, Alexander Schwarzenboeck, Johannes Schulze, Axel Eickhoff

Rolf Teschke, Alexander Schwarzenboeck, Axel Eickhoff, Department of Internal Medicine Ⅱ, Klinikum Hanau, Academic Teaching Hospital of the Medical Faculty of the Goethe University of Frankfurt/Main, D-63450 Hanau, Germany
Albrecht Wolff, Department of Internal Medicine Ⅱ, Division of Gastroenterology, Hepatology and Infectious Diseases, Friedrich Schiller University Jena, D-07743 Jena, Germany
Christian Frenzel, Department of Medicine Ⅰ, University Medical Center Hamburg Eppendorf, 20246 Hamburg, Germany
Johannes Schulze, Institute of Industrial, Environmental and Social Medicine, Medical Faculty, Goethe University, 60590 Frankfurt/Main, Germany
Author contributions: Teschke R and Eickhoff A provided substantial contributions to the conception and design; Wolff A, Frenzel C and Schwarzenboeck A contributed to the literature search and acquisition of relevant literature; Teschke R, Schulze J and Eickhoff A contributed to analysis and interpretation of the data; Teschke R contributed to drafting the article; Wolff A, Frenzel C, Schwarzenboeck A, Schulze J and Eickhoff A contributed to revising it critically for important intellectual content; all the authors contributed to final approval of the version to be published.
Correspondence to: Rolf Teschke, MD, Professor of Medicine, Department of Internal Medicine Ⅱ, Klinikum Hanau, Academic Teaching Hospital of the Medical Faculty of the Goethe University of Frankfurt/Main, Leimenstrasse 20, D-63450 Hanau, Germany. rolf.teschke@gmx.de
Telephone: +49-6181-21859 Fax: +49-6181-2964211
Received: August 2, 2013 Revised: November 11, 2013
Accepted: December 9, 2013
Published online: January 27, 2014

Abstract

Causality assessment of suspected drug induced liver injury (DILI) and herb induced liver injury (HILI) is hampered by the lack of a standardized approach to be used by attending physicians and at various subsequent evaluating levels. The aim of this review was to analyze the suitability of the liver specific Council for International Organizations of Medical Sciences (CIOMS) scale as a standard tool for causality assessment in DILI and HILI cases. PubMed database was searched for the following terms: drug induced liver injury; herb induced liver injury; DILI causality assessment; and HILI causality assessment. The strength of the CIOMS lies in its potential as a standardized scale for DILI and HILI causality assessment. Other advantages include its liver specificity and its validation for hepatotoxicity with excellent sensitivity, specificity and predictive validity, based on cases with a positive reexposure test. This scale allows prospective collection of all relevant data required for a valid causality assessment. It does not require expert knowledge in hepatotoxicity and its results may subsequently be refined. Weaknesses of the CIOMS scale include the limited exclusion of alternative causes and qualitatively graded risk factors. In conclusion, CIOMS appears to be suitable as a standard scale for attending physicians, regulatory agencies, expert panels and other scientists to provide a standardized, reproducible causality assessment in suspected DILI and HILI cases, applicable primarily at all assessing levels involved.

Key words: Drug induced liver injury; Drug hepatotoxicity; Herb induced liver injury; Herbal hepatotoxicity; Causality assessment

Core tip: We propose that the attending physicians caring for patients with assumed drug induced liver injury and herb induced liver injury should use the Council for International Organizations of Medical Sciences (CIOMS) scale for causality assessment. This approach includes the option of subsequent refinement of the CIOMS based results by expert panels and regulatory agencies. The use of the CIOMS scale as an identical

tool for all involved parties will allow early and prospective collection of all relevant data required for a valid causality assessment in clinical hepatology.

Teschke R, Wolff A, Frenzel C, Schwarzenboeck A, Schulze J, Eickhoff A. Drug and herb induced liver injury: Council for International Organizations of Medical Sciences scale for causality assessment. *World J Hepatol* 2014; 6(1): 17-32 Available from: URL: http://www.wjgnet.com/1948-5182/full/v6/i1/17.htm DOI: http://dx.doi.org/10.4254/wjh.v6.i1.17

INTRODUCTION

Drug induced liver injury (DILI) and herb induced liver injury (HILI) are complex diseases and often overdiagnosed[1-5]. An expert review of suspected DILI reports from primary and secondary care physicians to the UK Committee on the Safety of Medicine revealed that 47.1% of the cases were not DILI and that the misdiagnoses delayed arriving at the correct diagnoses, possibly worsening patient outcome[1]. Misdiagnosis was a common phenomenon in other DILI studies[2-4], including publications in which DILI was initially assumed, but hepatitis E virus infection later on evolved as the correct diagnosis[2,3]. Similarly, in a recent assessment of initially suspected HILI, correct diagnoses were missed in 278/573 cases, corresponding to 48.5%[5]. Given these frequencies because of insufficient case assessment, DILI and HILI represent major issues for physicians who care for patients with these diseases.

Physicians commonly are confronted with a wealth of published data about hepatic adverse drug and herb reactions and may use this information for evaluating the cases of their patients. Reviews addressed general aspects of DILI[6,7] or HILI[4,8-10], whereas other reports focused on various basic features like clinical course, prognosis, alternative causes, case definition and phenotype standardization[5,11-17]. They suggest a similar or identical clinical presentation of DILI and HILI, raising the question of whether HILI needs a separate term. However, major differences exist between DILI and HILI; DILI is caused by a single chemically characterized drug, whereas HILI is triggered by a chemical mixture constituted of the herbal extract, which often lacks the benefit of regulatory surveillance. Herbal product quality varies and is a major issue in HILI, adding to the complexity in evaluating causality for herbs. This may explain why HILI is considered as a poorly defined entity, is a neglected disease, and requires special attention.

Potential genetic risk factors and biomarkers, including micro-RNA, are presently being investigated to explain DILI and HILI disease[18-20]. These data provide promising clinical and scientific results but currently contribute little to diagnose DILI or HILI correctly and in time, or to exclude alternative causes. Recognizing that the best approach is still not available in clinical practice, the physician needs a pragmatic guideline to quickly evaluate suspicious cases and reach a conclusive diagnosis. This is at present best achieved by the combination of clinical judgement and a liver specific causality assessment algorithm like the CIOMS (Council for International Organizations of Medical Sciences) scale[21,22], as has been summarized recently[10,14,23-25]. For DILI and HILI case reports, the CIOMS scale based on international consensus meetings[21,22,26,27] is the commonly applied method to assess causality[4,5,10,14,23,24,28,29]. In clinical practice, causality assessment of suspected hepatotoxicity is hampered by the lack of a standardized approach, which is applicable to all levels of causality assessment[4,14,24] and requires simplicity of the assessment method rather than complexity to evaluate DILI and HILI cases.

This review analyzes the suitability of the liver specific CIOMS scale for causality assessment in DILI and HILI cases as a standard for attending physicians, regulatory agencies, expert panels and the scientific community. It focuses on the characteristic features of the CIOMS scale, discusses strengths and weaknesses, and suggests approaches for the clinician who lacks a standby panel of DILI or HILI experts.

The PubMed database was searched for the following terms: drug induced liver injury; herb induced liver injury; DILI causality assessment; and HILI causality assessment. The literature search was done on June 4, 2013. Several hundreds of records were initially obtained, depending of the term used. The first 50 publications of each search were analyzed in depth for suitability in the analysis of the CIOMS scale quality, with numerous duplicated reports found in each category. The final compilation of evaluated publications consists of original papers, case series, case reports, consensus reports and review articles. All relevant reports were included in the reference list to be presented in this review. Analyzed reports were published between 1977 and 2013, preferentially within the last decade.

GENERAL ASPECTS

The liver specific and quantitative CIOMS scale was conceptualized and developed in consensus meetings organized at the request of the Council for International Organizations of Medical Sciences (CIOMS), with details published in 1993[21,22]. This CIOMS scale represented a breakthrough in DILI causality assessment methods and extended, specified and quantified the preceding qualitative RUCAM (Roussel Uclaf Causality Assessment Method) of 1988[26] and qualitative CIOMS method of 1990[27]. The basis for the CIOMS scale was provided by eight experts in hepatology from 6 countries and included J P Benhamou (France), J Bircher (Germany), G Danan (France), W C Maddrey (United States), J Neuberger (United Kingdom), F Orlandi (Italy), N Tygstrup (Denmark) and H J Zimmerman (United States)[21]. This expert panel evaluated DILI cases for case characteris-

tics, hepatotoxicity criteria, liver injury pattern and reexposure criteria, standardized DILI case assessment with specific, quantitative items[21], and the experts validated their method with established positive reexposure DILI case results[22]. The CIOMS scale was developed for assessment of a single drug containing a synthetic product and may be used for a single herb containing multiple chemical constituents, but does not allow causality attribution to a specific constituent. The scale is a learning system and not immutable; room for improvement and refinement of the CIOMS scale has been outlined[29], with modifications of the CIOMS scale based on improved diagnostic instruments[14].

STRENGTHS

Prospective use

Its prospective application enables the CIOMS scale to provide an early causality grading for patients with suspected DILI or HILI; its results can be adapted further to diagnostic and therapeutic measures. This scale is easily used as a bedside tool at a time the disease is developing (Tables 1 and 2). Results do not depend on expert opinion and are quickly available for trained physicians to decide whether DILI and/or HILI should be considered as relevant differential diagnoses due to their clinical experience. Assessment is best started on the day of suspecting DILI or HILI, with a continuous update of the required data and a change in the diagnostic and therapeutic concept if needed. Finally, a complete data set for presentation to regulatory agencies, expert panels and eventually for publication is obtained[24,30-33], including a checklist with additional data helpful in overall case evaluation and causality assessment (Table 3). Therefore, the CIOMS scale should be considered as a standard for causality assessment of DILI and HILI, both for the attending physician and later evaluation stages. Using one single assessment method at all evaluating levels allows comparison of different assessment outcomes.

Liver specificity

Liver specificity is a hallmark of the CIOMS scale, in contrast to liver unspecific causality assessment methods or ad hoc approaches[4,24]. The CIOMS items are specially tailored to liver injury and not applicable to liver unrelated adverse drug reactions[24]. All current core elements of hepatotoxicity are considered in the CIOMS scale (Tables 1 and 2): time to onset of increased liver values or symptoms from the beginning and cessation of the drug/herb; course of liver enzymes after cessation; risk factors such as alcohol, age and pregnancy; comedication with other drugs/herbs; search for alternative causes, previously known drug/herb hepatotoxicity; and response to unintentional reexposure[21-25] based on specific criteria (Table 4). The individual items are transparent and facilitate quick and precise answers.

The CIOMS scale is structured and all its items undergo quantitative rather than qualitative assessment and scoring (Tables 1 and 2)[4,5,10,14,21,23,24,29]. Each item is weighted with specific scores based on the answer. The sum of the individual scores gives a final score that may range from -9 to +14 points, allowing for sufficient discrimination. The final score provides causality levels for the individual synthetic drug or herb as highly probable, probable, possible, unlikely or excluded (Tables 1 and 2)[12,24,30-32].

Hepatotoxicity definition

The international CIOMS expert panel defined liver injury in its consensus report as increased alanine aminotransferase (ALT) and/or alkaline phosphatase (ALP) activities of at least 2N, with N as the upper limit of normal[21]. Conversely, the consensus of the international DILI Expert Working Group with participants from Europe, the United States and Japan raised the ALT cut off point to 5N or 3N if total bilirubin values exceeded 2N and considered the 2N of ALP as an appropriate definition criterion[14]. Whereas the DILI Expert Working Group recommendations were based on expert opinion alone[14], those of the CIOMS expert panel were derived from both expert opinion and assessment of reference reexposure DILI cases[21,22].

Raising the ALT cut off to 5N increases the specificity of the hepatotoxicity causality assessment[24], eliminates false positive cases and substantiates hepatotoxicity causality at a higher level of probability[16,24]. The lower threshold of ALT > 2N will include multiple cases with nonspecific enzyme increases and requires more stringent exclusion of causes unrelated to drug(s) and herb(s)[24]. Also for low threshold N values, the inclusion rate of alternative diagnoses must be higher; false positive fulfilment of a hepatotoxicity definition results in high numbers of misattributed cases due to overdiagnosing and overreporting[8,12,17,24,34-48]. This phenomenon is illustrated in a recent HILI study where initial ALT values were available in only 8/22 cases (36%), including 3 cases with a range of 50-69 U/L serum activity[36]. None withstanding, regulatory assessment attributed a possible causality for the incriminated herb to all 22 cases[36,42]. In other spontaneous case collections, initial ALT values were available in 5/24 cases (21%)[35], 19/22 cases (86%)[37], 12/15 cases (80%)[38], and 7/13 cases (54%)[39]. The corresponding figures for ALT in published case reports of HILI were 16/16 cases (100%)[35], 21/21 cases (100%)[32], and 5/8 cases (63%)[33]. ALT values were included in DILI reports for amoxicillin/clavulanic acid, troglitazone, pioglitazone and montelukast in 11% to 88% of the cases, which were not further scored for causality by the Drug Induced Liver Injury Network (DILIN)[6]. ALT underreporting is therefore an issue for both DILI and HILI.

Other arguments merit further considerations. An ALT cut off point of 5N may not be applicable to some types of chronic liver injury like methotrexate liver fibrosis or nodular regenerative hyperplasia; misinterpretation is also possible in some forms of acute liver injury by mitochondrial toxicity in cases of valproate or

Table 1 Council for International Organizations of Medical Sciences scale for the hepatocellular type of injury and cholestatic or mixed type of injury in drug induced liver injury and herb induced liver injury cases

Items for hepatocellular injury	Score	Result
1 Time to onset from the beginning of the drug/herb		
5-90 d (rechallenge: 1-15 d)	2	-
< 5 or > 90 d (rechallenge: > 15 d)	1	-
Alternative: Time to onset from cessation of the drug/herb		
≤ 15 d (except for slowly metabolized chemicals: > 15 d)	1	-
2 Course of ALT after cessation of the drug/herb		
Percentage difference between ALT peak and N		
Decrease ≥ 50 % within 8 d	3	-
Decrease ≥ 50 % within 30 d	2	-
No information or continued drug/herb use	0	-
Decrease ≥ 50 % after the 30th day	0	-
Decrease < 50 % after the 30th day or recurrent increase	-2	-
3 Risk factors		
Alcohol use (drinks/d: > 2 for women, > 3 for men)	1	-
Alcohol use (drinks/d: ≤ 2 for women, ≤ 3 for men)	0	-
Age ≥ 55 yr	1	-
Age < 55 yr	0	-
4 Concomitant drug(s) or herbs(s)		
None or no information	0	-
Concomitant drug or herb with incompatible time to onset	0	-
Concomitant drug or herb with compatible or suggestive time to onset	-1	-
Concomitant drug or herb known as hepatotoxin and with compatible or suggestive time to onset	-2	-
Concomitant drug or herb with evidence for its role in this case (positive rechallenge or validated test)	-3	-
5 Search for non drug/herb causes	Tick if negative	-
Group Ⅰ (6 causes)		
Anti-HAV-IgM	□	-
HBsAg, anti-HBc-IgM, HBV-DNA	□	-
Anti-HCV, HCV-RNA	□	-
Hepatobiliary sonography/colour doppler sonography of liver vessels/endosonography/CT/MRC	□	-
Alcoholism (AST/ALT ≥ 2)	□	-
Acute recent hypotension history (particularly if underlying heart disease)	□	-
Group Ⅱ (6 causes)		
Complications of underlying disease(s) such as sepsis, autoimmune hepatitis, chronic hepatitis B or C, primary biliary cirrhosis or sclerosing cholangitis, genetic liver diseases	□	-
Infection suggested by PCR and titer change for CMV (anti-CMV-IgM, anti-CMV-IgG)	□	-
EBV (anti-EBV-IgM, anti-EBV-IgG)	□	-
HEV (anti-HEV-IgM, anti-HEV-IgG)	□	-
HSV (anti-HSV-IgM, anti-HSV-IgG)	□	-
VZV (anti-VZV-IgM, anti-VZV-IgG)	□	-
Evaluation of group Ⅰ and Ⅱ		
All causes-groups Ⅰ and Ⅱ - reasonably ruled out	2	-
The 6 causes of group Ⅰ ruled out	1	-
5 or 4 causes of group Ⅰ ruled out	0	-
Less than 4 causes of group Ⅰ ruled out	-2	-
Non drug or herb cause highly probable	-3	-
6 Previous information on hepatotoxicity of the drug/herb		
Reaction labelled in the product characteristics	2	-
Reaction published but unlabelled	1	-
Reaction unknown	0	-
7 Response to unintentional readministration		
Doubling of ALT with the drug/herb alone, provided ALT below 5N before reexposure	3	-
Doubling of ALT with the drug(s) and herb(s) already given at the time of first reaction	1	-
Increase of ALT but less than N in the same conditions as for the first administration	-2	-
Other situations	0	-
Total score for patient		

The CIOMS scale is based on the original CIOMS scale[21] and was adapted from previous modifications[4,14,23,24,44,45]. The above items specifically refer to the hepatocellular type of injury rather than to the cholestatic or mixed type (shown in Table 2). Regarding risk factor of alcohol use, 1 drink commonly contains about 10 g ethanol and details were discussed recently[14,44,45]. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CIOMS: Council for International Organizations of Medical Sciences; CMV: Cytomegalovirus; CT: Computer tomography; DILI: Drug induced liver injury; EBV: Epstein Barr virus; HAV: Hepatitis A virus; HBc: Hepatitis B core; HBsAg: Hepatitis B antigen; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HEV: Hepatitis E virus; HILI: Herb induced liver injury; HSV: Herpes simplex virus; MRC: Magnetic resonance cholangiography; N: Upper limit of the normal range; VZV: Varicella zoster virus. Total score and resulting causality grading: ≤ 0: Excluded; 1-2: Unlikely; 3-5: Possible; 6-8: Probable; ≥ 9: Highly probable.

fialuridine hepatotoxicity[14]. Aspartate aminotransferase (AST) activities may be used instead if ALT activities are unavailable[14,44,45] and other pathologies for AST increases are excluded[14]. ALP increases should be paral-

Table 2 Council for International Organizations of Medical Sciences scale for the cholestatic or mixed type of injury and cholestatic or mixed type of injury in drug induced liver injury and herb induced liver injury cases

Items for cholestatic or mixed injury	Score	Result
1 Time to onset from the beginning of the drug/herb		
5-90 d (rechallenge: 1-90 d)	2	-
< 5 or > 90 d (rechallenge: > 90 d)	1	-
Alternative: Time to onset from cessation of the drug/herb		
≤ 30 d (except for slowly metabolized chemicals: > 30 d)	1	-
2 Course of ALP after cessation of the drug/herb		
Percentage difference between ALP peak and N		
Decrease ≥ 50 % within 180 d	2	-
Decrease < 50 % within 180 d	1	-
No information, persistence, increase, or continued drug/herb use	0	-
3 Risk factors		
Alcohol use (drinks/d: > 2 for women, > 3 for men) or pregnancy	1	-
Alcohol use (drinks/d: ≤ 2 for women, ≤ 3 for men)	0	-
Age ≥ 55 yr	1	-
Age < 55 yr	0	-
4 Concomitant drug(s) or herbs(s)		
None or no information	0	-
Concomitant drug or herb with incompatible time to onset	0	-
Concomitant drug or herb with compatible or suggestive time to onset	-1	-
Concomitant drug or herb known as hepatotoxin and with compatible or suggestive time to onset	-2	-
Concomitant drug or herb with evidence for its role in this case (positive rechallenge or validated test)	-3	-
5 Search for non drug/herb causes	Tick if negative	-
Group Ⅰ (6 causes)		
Anti-HAV-IgM	□	-
HBsAg, anti-HBc-IgM, HBV-DNA	□	-
Anti-HCV, HCV-RNA	□	-
Hepatobiliary sonography/colour doppler sonography of liver vessels/endosonography/CT/MRC	□	-
Alcoholism (AST/ALT ≥ 2)	□	-
Acute recent hypotension history (particularly if underlying heart disease)	□	-
Group Ⅱ (6 causes)		
Complications of underlying disease(s) such as sepsis, autoimmune hepatitis, chronic hepatitis B or C, primary biliary cirrhosis or sclerosing cholangitis, genetic liver diseases	□	-
Infection suggested by PCR and titer change for CMV (anti-CMV-IgM, anti-CMV-IgG)	□	-
EBV (anti-EBV-IgM, anti-EBV-IgG)	□	-
HEV (anti-HEV-IgM, anti-HEV-IgG)	□	-
HSV (anti-HSV-IgM, anti-HSV-IgG)	□	-
VZV (anti-VZV-IgM, anti-VZV-IgG)	□	-
Evaluation of group Ⅰ and Ⅱ		
All causes-groups Ⅰ and Ⅱ - reasonably ruled out	2	-
The 6 causes of group Ⅰ ruled out	1	-
5 or 4 causes of group Ⅰ ruled out	0	-
Less than 4 causes of group Ⅰ ruled out	-2	-
Non drug or herb cause highly probable	-3	-
6 Previous information on hepatotoxicity of the drug/herb		
Reaction labelled in the product characteristics	2	-
Reaction published but unlabelled	1	-
Reaction unknown	0	-
7 Response to unintentional readministration		
Doubling of ALP with the drug/herb alone, provided ALP below 5N before reexposure	3	-
Doubling of ALP with the drug(s) and herb(s) already given at the time of first reaction	1	-
Increase of ALP but less than N in the same conditions as for the first administration	-2	-
Other situations	0	-
Total score for patient		

The CIOMS scale presented in this table is designed specifically for the cholestatic or mixed type of liver injury rather than for the hepatocellular type, which differs in a few items and is presented separately in Table 1. Additional details and abbreviations are provided in the legend of Table 1. Abbreviation: ALP, Alkaline phosphatase. Total score with resulting causality grading: ≤ 0, excluded; 1-2, unlikely; 3-5, possible; 6-8, probable; ≥ 9, highly probable.

leled by γ-glutamyltranspeptidase (γGT) to rule out isolated increases of ALP activities due to bone rather than hepatobiliary disease. However, γGT alone is not an appropriate parameter for liver cell injury[14,36], contrary to published claims[42]. In addition, isolated hyperbilirubinemia is not DILI or HILI specific and may be caused by Gilbert's syndrome[1,14].

Liver injury pattern

The CIOMS scale takes into account divergent laboratory constellations of the liver injury pattern in the hepatocellular and the cholestatic type of liver injury and

Table 3 Data checklist for drug induced liver injury and herb induced liver injury diagnosis assessment

Items to be assessed	Information obtained			Individual result
	Yes	No	Partial	
Brand name with batch number and expiration date	□	□	□	-
Indication of drug/herb use	□	□	□	-
Begin of symptoms leading to drug/herb treatment	□	□	□	-
Daily dose	□	□	□	-
Application form of drug/herb product	□	□	□	-
Exact date of drug/herb start	□	□	□	-
Exact date of drug/herb end	□	□	□	-
Exact dates of emerging new symptoms after drug/herb start in chronological order	□	□	□	-
Exact date of initially increased liver values	□	□	□	-
Time frame of challenge	□	□	□	-
Time frame of latency period	□	□	□	-
Time frame of dechallenge	□	□	□	-
Verification of temporal association	□	□	□	-
Exclusion of temporal association	□	□	□	-
Gender, age, body weight, height, BMI	□	□	□	-
Ethnicity, profession	□	□	□	-
Preexisting general diseases with past medical history and actual assessment	□	□	□	-
Preexisting liver diseases with past medical history and actual assessment regarding	□	□	□	-
Risk factors such as age and alcohol	□	□	□	-
Alcohol use with quantification	□	□	□	-
Comedication by synthetic drugs, herbal drugs, herbal and other dietary supplements with all details of product, daily dose, exact dates of start and end of use, indication	□	□	□	-
ALT value initially including exact date and normal range	□	□	□	-
ALT values during dechallenge at least on days 8 and 30, and later on, with exact dates	□	□	□	-
ALT values during dechallenge to exclude a second peak, with exact dates	□	□	□	-
ALT normalization with exact date and actual value	□	□	□	
ALP value initially including exact date and normal range	□	□	□	-
ALP values during dechallenge at least on days 8 and 30, and later on, with exact dates	□	□	□	-
ALP values during dechallenge to exclude a second peak, with exact dates	□	□	□	-
ALP normalization with exact date and actual value	□	□	□	-
AST value initially including normal range	□	□	□	-
Laboratory criteria for hepatotoxicity	□	□	□	-
Laboratory criteria for injury pattern	□	□	□	-
Liver and biliary tract imaging including hepatobiliary sonography, CT, MRT, MRC	□	□	□	-
Color Doppler sonography of liver vessels	□	□	□	-
Unintended reexposure	□	□	□	-
Known hepatotoxicity caused by the drug/herb	□	□	□	-
Other possible causes, consideration and exclusion	□	□	□	-
Hepatitis A - Anti-HAV-IgM	□	□	□	-
Hepatitis B - HBsAg, anti-HBc-IgM, HBV-DNA	□	□	□	-
Hepatitis C - Anti-HCV, HCV-RNA	□	□	□	-
Hepatitis E - Anti-HEV-IgM, anti-HEV-IgG, HEV-RNA	□	□	□	-
Cytomegalovirus (CMV) - CMV-PCR, titer change for anti-CMV-IgM and anti-CMV-IgG	□	□	□	-
Epstein Barr virus (EBV) - EBV-PCR, titer change for anti-EBV-IgM and anti-EBV-IgG	□	□	□	-
Herpes simplex virus (HSV) - HSV-PCR, titer change for anti-HSV-IgM and anti-HSV-IgG	□	□	□	-
Varicella zoster virus (VZV) - VZV-PCR, titer change for anti-VZV-IgM and anti-VZV-IgG	□	□	□	-
Other virus infections - specific serology of Adenovirus, coxsackie-B-Virus, echovirus, measles virus, rubella virus, flavivirus, arenavirus, filovirus, parvovirus, HIV, and others	□	□	□	-
Other infectious diseases - specific assessment of bacteria (such as campylobacter, coxiella, leptospirosis, listeria, salmonella, treponema pallidum), fungi, parasites, worms, tropical diseases, and others	□	□	□	-
Autoimmune hepatitis (AIH) type Ⅰ - Gamma globulins, ANA, SMA, AAA, SLA/LP	□	□	□	-
Autoimmune hepatitis (AIH) type Ⅱ - Gamma globulins, anti-LKM-1 (CYP 2D6), anti-LKM-2 (CYP 2C9), anti-LKM-3	□	□	□	-
Primary biliary cirrhosis (PBC) - AMA, anti PDH-E2	□	□	□	-
Primary sclerosing cholangitis (PSC) - p-ANCA, MRC	□	□	□	-
Autoimmune cholangitis (AIC) - ANA, SMA	□	□	□	-
Overlap syndromes - see AIH, PBC, PSC, and AIC	□	□	□	-
Non alcoholic steatohepatitis (NASH) - BMI, insulin resistance, hepatomegaly, echogenicity of the liver	□	□	□	-
Alcoholic liver disease (ALD) - patient's history, clinical and laboratory assessment, sonography	□	□	□	-
Drug/herb induced liver injury - patient's history, clinical and laboratory assessment, sonography, use of the CIOMS scale	□	□	□	-
Toxin Screening - cocaine, ecstasy and other amphetamines	□	□	□	-
Rare intoxications - toxin screening for household and occupational toxins	□	□	□	-
Hereditary hemochromatosis - serum ferritin, total iron-binding capacity, genotyping for C2824 and H63D mutation, hepatic iron content	□	□	□	-

Wilson's disease - copper excretion (24 h urine), ceruloplasmin in serum, free copper in serum, coombs-negative hemolytic anemia, hepatic copper content, Kayser-Fleischer-Ring, neurologic-psychiatric work-up, genotyping	□	□	□	-
Porphyria - corphobilinogen in urine, total porphyrines in urine	□	□	□	-
α1 - antitrypsin deficiency - α1- Antitrypsin in serum	□	□	□	-
Biliary diseases - clinical and laboratory assessment, hepatobiliary sonography, endosonography, CT, MRT, MRC	□	□	□	-
Pancreatic diseases - clinical and laboratory assessment, sonography, CT, MRT	□	□	□	-
Celiac disease - TTG antibodies, endomysium antibodies, duodenal biopsy	□	□	□	-
Anorexia nervosa - clinical context	□	□	□	-
Parenteral nutrition - clinical context	□	□	□	-
Cardiopulmonary diseases with shock liver (cardiac hepatopathy, ischemic hepatitis) - cardiopulmonary assessment of congestive heart disease, myocardial infarction, cardiomyopathy, cardiac valvular dysfunction, pulmonary embolism, pericardial diseases, arrhythmia, hemorrhagic shock, and various other conditions	□	□	□	-
Addison's disease - plasma cortisol	□	□	□	-
Thyroid diseases - TSH basal, T4, T3	□	□	□	-
Grand mal seizures - clinical context of epileptic seizure (duration > 30 min)	□	□	□	-
Heat stroke - shock, hyperthermia	□	□	□	-
Polytrauma - shock, liver injury	□	□	□	-
Systemic diseases - specific assessment of M. Boeck, amyloidosis, lymphoma, other malignant tumors, sepsis, and others	□	□	□	-
Graft *vs* host disease - clinical context	□	□	□	-
Other diseases - clinical context	□	□	□	-

This checklist is far from complete and considered as a reminder for the physician. Some listed liver diseases like AIH require a liver biopsy to establish the diagnosis. Few elements are not directed to causality assessment but are important for overall case evaluation. AAA: Anti-actin antibodies; AMA: Antimitochondrial antibodies; ANA: Antinuclear antibodies; BMI: Body mass index; CT: Computed tomography; CYP: Cytochrome P450; HAV: Hepatitis A virus; HBc: Hepatitis B core; HBsAg: Hepatitis B antigen; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HEV: Hepatitis E virus; HILI: Herb induced liver injury; HIV: Human immunodeficiency virus; LKM: Liver kidney microsomes; LP: Liver-pancreas antigen; MRC: Magnetic resonance cholangiography; MRT: Magnetic resonance tomography; p-ANCA: Perinuclear antineutrophil cytoplasmatic antibodies; PDH: Pyruvate dehydrogenase; PCR: Polymerase chain reaction; SLA: Soluble liver antigen; SMA: Smooth muscle antibodies; TSH: Thyroid stimulating hormone; TTG: Tissue transglutaminase.

Table 4 Conditions of unintentional reexposure tests in drug induced liver injury and herb induced liver injury cases

Reexposure test result	Hepatocellular type of liver injury		Cholestatic or mixed type of liver injury	
	ALTb	ALTr	ALPb	ALPr
Positive	< 5N	⩾ 2ALTb	< 5N	⩾ 2ALPb
Negative	< 5N	< 2ALTb	< 5N	< 2ALPb
Negative	⩾ 5N	⩾ 2ALTb	⩾ 5N	⩾ 2ALPb
Negative	⩾ 5N	< 2ALTb	⩾ 5N	< 2ALPb
Negative	⩾ 5N	NA	⩾ 5N	NA
Uninterpretable	< 5N	NA	< 5N	NA
Uninterpretable	NA	NA	NA	NA

Conditions and criteria for an unintentional reexposure test are described in previous reports[4,21,22,24,26,27]. **Accordingly, required data for the hepatocellular type of liver injury are the ALT levels just before reexposure, designed as baseline ALT or ALTb, and the ALT levels during reexposure, designed as ALTr. Response to reexposure is positive, if both criteria are met: first, ALTb is below 5N with N as the upper limit of the normal value, and second ALTr ⩾ 2ALTb. Other variations lead to negative or uninterpretable results. For the cholestatic or mixed type of liver injury, corresponding values of ALP are to be used rather than of ALT. ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; NA: Not available.**

therefore provides two different subscales[21,23,24] for the hepatocellular type of injury (Table 1) and for the cholestatic or mixed type (Table 2). These types are differentiated by the ratio R, calculated as the ALT/ALP activity measured at the time liver injury is suspected, with both activities expressed as multiples of N[21,24]. Injury is hepatocellular, if only ALT > 2N, alternatively if R ⩾ 5; cholestatic injury is assumed, if only ALP > 2N or R ⩽ 2; mixed damage is prevalent, if ALT > 2N and ALP is increased, with R > 2 and R < 5[21,23,24]. Of note, R may vary during the later course of the liver injury independent from the initial attribution of damage type.

Time to onset from the beginning of the drug/herb

Clear challenge criteria are defined with a time frame between beginning of the drug/herb use as the first day of intake and the onset of increased liver enzymes or symptoms at the time of ongoing use, with a high score for 5-90 d and a lower one for < 5 d or > 90 d (Tables 1 and 2). If drug/herb use has been terminated prior to the onset of challenge criteria, then this specific condition must be considered and scored exclusively. Scoring is only possible when the onset occurs within 15 d after cessation for the hepatocellular injury (Table 1) or 30 d for the cholestatic or mixed type (Table 2), a longer interval commonly excludes causality (Tables 1 and 2). An exemption is provided for slowly metabolized chemicals like amiodarone, leflunomide and clavulanate[44,45]; no definitive time frame can be provided in these cases due to varying half lives. The time frame of challenge and latency period were neither specified nor individually scored by other causality assessment methods[4,24], including the DILIN method[49,50].

Course of liver enzymes after cessation of the drug/herb

Precise dechallenge criteria are cornerstones of the CIOMS scale and facilitate causality assessment (Tables 1 and 2). In analogy to the periods mentioned, the physician can easily determine relevant future time points for repeated liver enzyme tests. When dechallenge data are missing in retrospective analyses, the CIOMS scale considers this and provides 0, but not negative points, so

Table 5 Frequency of risk factors of alcohol and age among herb induced liver injury patients

HILI study cohort	Total study cases (*n*)	Cases scored with risk factors (*n*)			Total cases scored with risk factors *n* (%)	Cases with references
		Alcohol	Age	Alcohol + Age		
Kava	26	0	6	1	7 (26.9)	Cases 2, 4, 10, 17, 20, 24, 26[12]
Kava	5	0	3	0	3 (60.0)	Cases 1-3[46]
Ayurvedic herbs	1	0	1	0	1 (100.0)	Case 1[30]
Black cohosh	4	2	1	0	3 (75.0)	Cases 2, 3, 4[47]
Black cohosh	9	1	1	0	2 (22.2)	Cases 4, 9[48]
Black cohosh	22	4	2	0	6 (27.3)	Cases 2, 8, 10, 16, 17, 21[36]
Greater Celandine	22	1	9	0	10 (45.5)	Cases 3, 5, 8, 11, 14-18, 21[37]
Greater Celandine	21	0	7	0	7 (33.5)	Cases 4,9, 11, 16-18, 20[32]
Pelargonium sidoides	15	0	3	0	3 (20.0)	Cases 1, 7, 14[38]
Pelargonium sidoides	13	0	7	0	7 (53.9)	Cases 2, 3, 5, 8, 9, 11, 13[39]
Herbalife	8	0	3	0	3 (37.5)	Cases 1, 2, 4[33]
Total	146	8	43	1	52 (35.6)	

The study cohort consisted of 146 herb induced liver injury patients patients assessed for the frequency of the risk factors alcohol and age ⩾ 55 years. In 52/146 cases (35.6%), risk factors were evident.

that the overall score may still present a probable causality level. Of note, the dechallenge time frame was not specifically considered or scored by the DILIN method[49,50] or by virtually any of the other methods[4,24].

Risk factors

The consensus report of the international CIOMS expert panel considered alcohol and age ⩾ 55 years as risk factors each scoring +1 point (Tables 1 and 2)[21], as suggested by DILI cases with positive reexposure[21,22]. The international DILI Expert Working Group specified alcohol intake of > 2 drinks per day (> 14 units/week) in women and > 3 drinks per day (21 units/week) in men as the lower threshold for alcohol intake as a risk factor (Tables 1 and 2)[14]. This limit is in line with the recommendations of NIH LiverTox equalling 1 drink to 10 g ethanol[44,45].

The impact of including alcohol as a risk factor on the overall CIOMS scoring was negligible as only 9/146 patients (6%) of a HILI study cohort were allotted an alcohol related scoring point (Table 5)[12,30,32,36-39,46-48]. In these 9 patients, CIOMS causality grading was changed in only one case (patient 16) and unchanged in the other 8 cases (patients 2, 13, 14, 17, 20, 21, 22, 32) (Table 6). In the single case (patient 16), alcohol as risk factor raised the overall CIOMS scoring from 0 to +01 point, *i.e.*, from excluded to unlikely causality (Table 6). Therefore, alcohol per se as risk factor upgrades the CIOMS causality level in virtually none of the cases in this study cohort.

Age ⩾ 55 years was as a risk factor in 44/146 cases (30%) of the analyzed HILI study cohort (Table 5)[12,30,32,36-39,46-48]. In 35/44 patients, the overall CIOMS causality grading remained unchanged whether or not age as a risk factor was included in the CIOMS scale scoring (Table 6). Deletion of age as a risk factor reduced the overall CIOMS grading by one causality level in 9/44 patients, *i.e.*, from unlikely to excluded in 5 cases (patients 1, 3, 15, 42, 43), from highly probable to probable in 1 case (patient 23), and from probable to possible in 3 cases (patients 9, 25, 34). Therefore, within this cohort the risk factor age upgraded the causality levels only marginally, which appears to have no clinical relevance. Overall, age as a risk factor has a limited impact on the final causality gradings by the CIOMS scale.

Risk factors are not considered and/or not scored by various other methods[4,24,49,50], including the DILIN method[49,50]. Conversely, the international DILI Expert Group also accepts the risk factors defined in the CIOMS scale, with modified specifications and limitations, if risk factors for hepatotoxicity are present in addition to those listed in the CIOMS algorithm[14].

Concomitant drug(s) and herbs(s)

Concomitant drugs and herbs are individually assessed for temporal association and hepatotoxic potency (Tables 1 and 2). For reasons of comparison and transparency, each comedicated drug or herb requires a separate analysis by the complete CIOMS scale. This is feasible and easily tabulated (Table 7)[30,47,48]. In patients with multiple drug or herb intakes, causality should be attributed primarily to the product with the highest score.

Search for non drug/herb causes

In this section, the CIOMS scale considers the clinically most relevant alternative causes (Tables 1 and 2). There is no difference in alternative causes made between the two types of liver injury, avoiding the need of subsequent reassessment, if the laboratory based typology changes during the clinical course[45]. Complications of underlying disease(s) are exemplified, such as sepsis, autoimmune hepatitis, chronic hepatitis B or C, primary biliary cirrhosis and sclerosing cholangitis and genetic liver diseases (Tables 1 and 2), in accordance with recent suggestions[45]. Other rare alternative causes are included in a checklist of differential diagnoses as a reminder for the clinician in case of unclear clinical diagnosis (Table 3)[24].

To improve its performance when used as an investigational tool, criteria for competing liver injury causes have been proposed for the CIOMS scale[14,29,44,45,49,50]

Table 6 Changes of the Council for International Organizations of Medical Sciences gradings with considering the risk factors

HILI study	Scored risk		CIOMS assessment with RF	CIOMS assessment without RF	Grading change	Cases with references
	Alcohol	Age	Score/grading	Score/grading		
Kava	0	+	+1/Unlikely	0/Excluded	↓	Case 2[12]
Kava	+	+	-1/Excluded	-3/Excluded	0	Case 4[12]
Kava	0	+	+1/Unlikely	0/Excluded	↓	Case 10[12]
Kava	0	+	-1/Excluded	-2/Excluded	0	Case 17[12]
Kava	0	+	+8/Probable	+7/Probable	0	Case 20[12]
Kava	0	+	-1/Excluded	-2/Excluded	0	Case 24[12]
Kava	0	+	-1/Excluded	-2/Excluded	0	Case 26[12]
Kava	0	+	+5/Possible	+4/Possible	0	Case 1[46]
Kava	0	+	+6/Probable	+5/Possible	↓	Case 2[46]
Kava	0	+	+8/Probable	+7/Probable	0	Case 3[46]
Ayurvedic herbs	0	+	+8/Probable	+7/Probable	0	Case 1[30]
Black cohosh	0	+	-2/Excluded	-3/Excluded	0	Case 1[47]
Black cohosh	+	0	-2/Excluded	-3/Excluded	0	Case 2[47]
Black cohosh	+	0	-3/Excluded	-4/Excluded	0	Case 3[47]
Black cohosh	0	+	+1/Unlikely	0/Excluded	↓	Cases 4[48]
Black cohosh	+	0	+1/Unlikely	0/Excluded	↓	Case 9[48]
Black cohosh	+	0	-1/Excluded	2/Excluded	0	Case 2[36]
Black cohosh	0	+	-1/Excluded	-2/Excluded	0	Case 8[36]
Black cohosh	0	+	-1/Excluded	-2/Excluded	0	Case 10[36]
Black cohosh	+	0	0/Excluded	-1/Excluded	0	Case 16[36]
Black cohosh	+	0	0/Excluded	-1/Excluded	0	Case 17[36]
Black cohosh	+	0	-2/Excluded	-3/Excluded	0	Case 21[36]
Greater Celandine	0	+	+9/Highly probable	+8/Probable	↓	Case 2[37]
Greater Celandine	0	+	+10/Highly probable	+9/Highly probable	0	Case 5[37]
Greater Celandine	0	+	+6/Probable	+5/Possible	↓	Case 8[37]
Greater Celandine	0	+	+5/Possible	+4/Possible	0	Case 11[37]
Greater Celandine	0	+	+8/Probable	+7/Probable	0	Case 14[37]
Greater Celandine	0	+	+5/Possible	+4/Possible	0	Case 15[37]
Greater Celandine	0	+	-1/Excluded	-2/Excluded	0	Case 16[37]
Greater Celandine	0	+	+8/Probable	+7/Probable	0	Case 17[37]
Greater Celandine	0	+	0/Excluded	-1/Excluded	0	Case 18[37]
Greater Celandine	+	0	+4/Possible	+3/Possible	0	Case 21[37]
Greater Celandine	0	+	+5/Possible	+4/Possible	0	Case 4[32]
Greater Celandine	0	+	+6/Probable	+5/Possible	↓	Case 9[32]
Greater Celandine	0	+	+3/Possible	+2/Possible	0	Case 11[32]
Greater Celandine	0	+	+7/Probable	+6/Probable	0	Case 16[32]
Greater Celandine	0	+	+7/Probable	+6/Probable	0	Case 17[32]
Greater Celandine	0	+	+5/Possible	+4/Possible	0	Case 18[32]
Greater Celandine	0	+	+7/Probable	+6/Probable	0	Case 20[32]
Pelargonium sidoides	0	+	0/Excluded	-1/Excluded	0	Case 1[38]
Pelargonium sidoides	0	+	+2/Unlikely	+1/Unlikely	0	Case 7[38]
Pelargonium sidoides	0	+	+1/Unlikely	0/Excluded	↓	Case 14[38]
Pelargonium sidoides	0	+	+1/Unlikely	0/Excluded	↓	Case 2[39]
Pelargonium sidoides	0	+	+4/Possible	+3/Possible	0	Case 3[39]
Pelargonium sidoides	0	+	0/Excluded	-1/Excluded	0	Case 5[39]
Pelargonium sidoides	0	+	0/Excluded	-1/Excluded	0	Case 8[39]
Pelargonium sidoides	0	+	+2/Unlikely	+1/Unlikely	0	Case 9[39]
Pelargonium sidoides	0	+	+2/Unlikely	+1/Unlikely	0	Case 11[39]
Pelargonium sidoides	0	+	0/Excluded	-1/Excluded	0	Case 13[39]
Herbalife	0	+	+7/Probable	+6/Probable	0	Case 1[33]
Herbalife	0	+	+2/Unlikely	+1/Unlikely	0	Case 2[33]
Herbalife	0	+	+2/Unlikely	+1/Unlikely	0	Case 4[33]

Based on details described in Table 5, in all 52 patients with evident risks factors of alcohol, age ⩾ 55 years, or both, scores and Council for International Organizations of Medical Sciences (CIOMS) gradings with risk factors were compared with conditions without risk factor consideration. In 9 patients, there was a CIOMS downgrading when risk factors would not have been considered. RF: Risk factor.

and were included in the updated CIOMS scale (Tables 1 and 2)[24]. This update ensures correct diagnosis of alternative causes but was limited to details of hepatitis serology and hepatobiliary sonography, as specified by the current knowledge in the field and adapted to actual diagnostic methods[23,24]. The update of the original CIOMS scale substantially improved specificity, *i.e.*, exclusion of alternative causes by hepatitis serology. HBsAg and HBV-DNA quantification were added to distinguish HBV infection from immunization, as was hepatitis C virus (HCV)-RNA to correctly assess HCV infections. Also, clinical and/or biological parameters for cytomegalovirus (CMV), Epstein Barr virus (EBV) or herpes simplex virus (HSV) infection were vague or

Table 7 Council for International Organizations of Medical Sciences scale as an example with items required for causality assessment in a patient with herb induced liver injury by four different Indian Ayurvedic herbs

Items for hepatocellular injury	Possible score	Psoralea corylifolia	Acacia catechu	Eclipta alba	Vetivexia zizaniodis
1 Time to onset from the beginning of the herb 5-90 d (rechallenge: 1-15 d)	2				
< 5 or > 90 d (rechallenge: > 15 d)	1	1	1	1	1
Alternative: Time to onset from cessation of the herb					
≤ 15 d (except for slowly metabolized herbal chemicals: > 15 d)	1				
2 Course of ALT after cessation of the herb					
Percentage difference between ALT peak and N					
Decrease ≥ 50% within 8 d	3	3	3	3	3
Decrease ≥ 50% within 30 d	2				
No information or continued herbal use	0				
Decrease ≥ 50% after the 30th day	0				
Decrease < 50% after the 30th day or recurrent increase	-2				
3 Risk factors					
Alcohol use (drinks/d: > 2 for women, > 3 for men)	1				
Alcohol use (drinks/d: ≤ 2 for women, ≤ 3 for men)	0	0	0	0	0
Age ≥ 55 yr	1	1	1	1	1
Age < 55 yr	0				
4 Concomitant herbs(s) and drug(s)					
None or no information	0				
Concomitant herb or drug with incompatible time to onset	0				
Concomitant herb or drug with compatible or suggestive time to onset	-1	-1			
Concomitant herb or drug known as hepatotoxin and with compatible or suggestive time to onset	-2		-2	-2	-2
Concomitant herb or drug with evidence for its role in this case (positive rechallenge or validated test)	-3				
5 Search for non herb causes					
Group Ⅰ (6 causes)					
Anti-HAV-IgM		-	-	-	-
HBsAg, anti-HBc-IgM, HBV-DNA		-	-	-	-
Anti-HCV, HCV-RNA		-	-	-	-
Hepatobiliary sonography/colour Doppler sonography of liver vessels/ endosonography/CT/MRC		-	-	-	-
Alcoholism (AST/ ALT ≥ 2)		-	-	-	-
Acute recent hypotension history (particularly if underlying heart disease)		-	-	-	-
Group Ⅱ (6 causes)					
Complications of underlying disease(s) such as sepsis, autoimmune hepatitis, chronic hepatitis B or C, primary biliary cirrhosis or sclerosing cholangitis, genetic liver diseases		-	-	-	-
Infection suggested by PCR and titre change for		-	-	-	-
CMV (anti-CMV-IgM, anti-CMV-IgG)		-	-	-	-
EBV (anti-EBV-IgM, anti-EBV-IgG)		-	-	-	-
HEV (anti-HEV-IgM, anti-HEV-IgG)		-	-	-	-
HSV (anti-HSV-IgM, anti-HSV-IgG)		-	-	-	-
VZV (anti-VZV-IgM, anti-VZV-IgG)		-	-	-	-
Evaluation of group Ⅰ and Ⅱ					
All causes-groups Ⅰ and Ⅱ - reasonably ruled out	2	2	2	2	2
The 6 causes of group Ⅰ ruled out	1				
5 or 4 causes of group Ⅰ ruled out	0				
Less than 4 causes of group Ⅰ ruled out	-2				
Non herb cause highly probable	-3				
6 Previous information on hepatotoxicity of the herb					
Reaction labelled in the product characteristics	2				
Reaction published but unlabelled	1	1			
Reaction unknown	0		0	0	0
7 Response to unintentional readministration					
Doubling of ALT with the herb alone, provided ALT below 5N before reexposure	3				
Doubling of ALT with the herb(s) and drug(s) already given at the time of first reaction	1				
Increase of ALT but less than N in the same conditions as for the first administration	-2				
Other situations	0				
Total score for each individual herb used by the patient		7	5	5	5

The data of the patient with severe hepatotoxicity by four different Indian Ayurvedic herbs are derived from a published report[30], using the CIOMS scale for the hepatocellular type of liver injury (Table 1). The symbol of - signifies that this particular item has been evaluated and no abnormality was found. For the four herbs, the total score was either +7 (probable causality) or +5 (possible causality). Abbreviations see legend to Table 1.

unknown at the time of compilation[21] but specified in the updated CIOMS scale; also included and specified were infections by hepatitis E virus (HEV) and varicella zoster virus (VZV) (Tables 1 and 2)[24]. Specific diagnostic criteria include polymerase chain reaction detection and titer changes of the respective antibodies (IgM, IgG) for CMV, EBV, HEV, HSV and VZV infections. Hepatobiliary sonography was supplemented by color Doppler sonography, including assessments of the liver vessels, endosonography, computed tomography (CT) and magnetic resonance cholangiography (MRC), if these tests were indicated clinically (Tables 1 and 2). For comparison and method validation, causality has been evaluated in 101 hepatotoxicity cases by both the original and updated CIOMS scales, with identical causality results published in 6 studies[32,33,36-39]. Therefore, the updated CIOMS scale was validated and there is no need for further validation of the updated CIOMS scale versus the original CIOMS scale.

Previous information on hepatotoxicity of the drug/herb

Hepatotoxicity listed in the product information sheet must be checked; in addition, a quick literature search in PubMed will be sufficient to determine whether the observed reaction has been published before. Appropriate information may also be obtained from the NIH LiverTox database[44,45].

Response to unintentional readministration

To classify an unintentional reexposure test as positive, few criteria are required (Tables 1 and 2), as specified (Table 4)[21,22,24,26,27]. Although reexposure is an important domain, probable causality gradings with the CIOMS scale are achievable even in the absence of a reexposure (Table 7)[12,17,30-32,37].

Scoring system

Each item of the CIOMS scale receives an individual score and the sum of the individual scores provides the final score for the patient (Tables 1 and 2). With +14 down to -9 points, there is a wide range of the final scores, leading to the following causality levels: $\leqslant$ 0 points, excluded causality; 1-2, unlikely; 3-5, possible; 6-8, probable; and $\geqslant$ 9, highly probable (Tables 1 and 2)[21].

Sensitivity, specificity and predictive value

Cases with positive reexposure tests were proposed for validation of the CIOMS scale and used as gold standard[22]. Articles from two databanks were compiled with liver injury confirmed by a positive rechallenge. The mandatory information for inclusion in this series contained the type of liver injury, time interval between administration of the drug and occurrence of the reaction, and results of the positive response to readministration of the drug, in accordance with the conclusions of the International Consensus Meeting on drug induced liver injuries. For the final validation, 49 cases and 28 controls were assessed, as described in detail[22]. Most importantly, the discriminative power of the score was quantified in terms of sensitivity, specificity and predictive values. The cut off point was offset to maximize the combined sensitivity and specificity. Using +5 points as the cut off, sensitivity was 86%, specificity 89%, positive predictive value 93%, and negative predictive value 78% for the CIOMS causality assessment. In another study with 81 cases and 46 controls, sensitivity was 78% and specificity 100% for the CIOMS scale[51], confirming the validation of the CIOMS scale.

The interrater reliability of CIOMS assessment was good by one group[52] but mediocre by the DILIN group[49]. In the latter report, however, 40 cases going back to 1994 were studied. Uncertainties arose from numerous missing, incomplete or outdated medical reports and charts, especially for older cases. In particular, there were high rates (28%) of preexisting liver diseases like chronic hepatitis C virus infection, hemochromatosis and unspecified cirrhosis. Liver sonography was reported in 26/40 cases and found abnormal in 15/26 (58%). These data were nevertheless described as "best-case scenario"[49]. Considering these limitations and numerous confounding variables, poor case data quality likely results in mediocre assessment quality, including low interrater reliability[49]. Moreover, problematic data presentation by the principal assessor to external reviewers may have influenced the results as the external reviewers received only a subset of the case report forms and had no access to the original data of the cases[49]. Of interest, no proof has been provided that an expert group opinion improves the CIOMS assessment evaluation, at least according to recent comments and studies[11,49]. In another study comparing the CIOMS scale with the DILIN method, there was considerable interobserver variability in both methods[50].

Usage frequency

The CIOMS scale for hepatotoxicity assessment in its original or updated form[4,5,10,14,23,24,28,29] has been extensively used in epidemiological studies, clinical trials, case reports, case series, regulatory analyses and genotyping studies[4]. Additional efforts are still needed to reevaluate causality in most HILI reports for 60 different herbs and herbal products[53]. CIOMS based results were published by the DILIN group[49,50] and by the European Medicines Agency (EMA)[54]. Individual studies[10,16,55,56], the NIH LiverTox[44,45], the international DILI Expert Working Group[14], the Spanish Group for the Study of Drug-Induced Liver Disease[29], and the Hong Kong Herb-Induced Liver Injury Network (HK-HILIN)[57] provided further support for the CIOMS scale.

Among various causality assessment methods, the original and updated CIOMS scales were the preferred tools in cases of DILI[28] and HILI (Table 8)[5], seen for 573 cases from 23 HILI reports evaluating alternative causes[12,32,34,36-39,42,43,47,48,54,57-67].

Transparency

CIOMS based assessments should be reported or published as an original data set suitable for subsequent and independent assessments, rather than as final scores and

Table 8 Compilation of causality assessment methods used in suspected herb induced liver injury cases

Herbs/Herbal products	Ad hoc (*n*)	WHO (*n*)	CIOMS (*n*)	Naranjo (*n*)	DILIN (*n*)	KL (*n*)	Ref.
Kava	20						BfArM[58]
Kava		30					Denham *et al*[59]
Kava	20						Teschke *et al*[60]
Kava			36				Stickel *et al*[61]
Kava		80					Schmidt *et al*[62]
Greater Celandine	23						BfArM[63]
Black cohosh			31				EMA[54]
Herbalife products		12					Elinav *et al*[64]
Herbalife products		12					Schoepfer *et al*[65]
Kava			26				Teschke *et al*[12]
Black cohosh				30			Mahady *et al*[42]
Green tea				34			Sarma *et al*[43]
Black cohosh			4				Teschke *et al*[47]
Black cohosh			9				Teschke *et al*[48]
Kava			31				Teschke[34]
Hydroxycut					17		Fong *et al*[66]
Black cohosh			22				Teschke *et al*[36]
Greater Celandine			22				Teschke *et al*[37]
Herbalife products						20	Manso *et al*[67]
Various herbs			45				Chau *et al*[57]
Greater Celandine			21				Teschke *et al*[32]
Pelargonium sidoides			15				Teschke *et al*[38]
Pelargonium sidoides			13				Teschke *et al*[39]
Sum (*n*)	63	134	275	64	17	20	
Sum (percent)	11.00%	23.40%	48.00%	11.20%	3.00%	3.40%	

The data are derived from a study evaluating alternative causes in suspected HILI cases (n = 573) comprising the study cohort[5]. For the 275 CIOMS cases, causality assessment was performed with the updated CIOMS scale the original CIOMS scale, or both. Ad hoc: ad hoc approach; CIOMS: Council for International Organizations of Medical Sciences scale; DILIN: Drug Induced Liver Injury Network method; KL: Karch and Lasagna method; Naranjo: Naranjo scale; WHO: World Health Organization method.

corresponding causality levels, to improve data transparency. Scientists, editors and reviewers should strive to obtain appropriate CIOMS based details for all DILI and HILI case reports. This can easily be achieved since the CIOMS scale provides all items in tabulated form for each individual case (Tables 1, 2 and 7). These forms may be communicated as a spontaneous report to regulatory agencies and expert panels or presented for publication to scientific journals as a case report[24,30,31] or case series[12,24,32]. This tabulation is a good basis for further regulatory or scientific assessments and discussions. For regulatory and expert based assessments, there is no need for other causality assessment algorithms to be used subsequently since CIOMS based data are also amenable to regulatory and expert panel evaluations.

Comparison to precursor scales

The CIOMS scale resulted from intensive expert discussions[21], integrating medical progress and improving the initial qualitative RUCAM[26] and the qualitative CIOMS method[27]. The qualitative RUCAM represented the first objective attempt to assess causality in drug induced liver injury and considered some characteristic features of liver injury, but it had a qualitative rather than a quantitative approach[26]. As an improved version of the qualitative RUCAM[26], the qualitative CIOMS method differentiated the hepatocellular, the cholestatic and the mixed type of liver injury[27]. However, both the qualitative RUCAM[26] and the qualitative CIOMS method[27] were not quantitative, as opposed to the current quantitative CIOMS scale[21] that is now the preferred tool[24].

Other liver specific methods

The scale of Maria and Victorino (MV)[68] was developed to improve upon the CIOMS scale by deleting laboratory items and adding clinical elements, along with simplifying and changing the relative weight of elements in their algorithm[23,44,45]. No data are available for specificity, sensitivity, positive and negative predictive values for the MV scale[68]. Compared to the original CIOMS scale[21], the MV scale[68] showed shortcomings and the results are not equivalent, causing major concern[10,14,23,24,29,44,45,69-71]. This may explain why the MV scale was used in a few DILI studies[1,72,73], but not in 38 other publications of DILI cases[28] or in 23 publications of HILI cases[5]. The MV scale is not commonly recommended for assessing causality in assumed DILI and HILI cases and is certainly no substitute for the CIOMS scale[24].

The TTK scale[25], named for the first three authors Takikawa, Takamori, Kumagi *et al*[74], is a modification of the CIOMS scale[21] with different evaluations of the chronology, exclusion of comedication, inclusion of the drug lymphocyte stimulation test (DLST) and of eosinophilia in their assessment system[74,75]. The TTK scale is widely used in Japan[74], as recently reviewed[75]. In other countries, this scale is not or rarely

considered[5,10,14,24,28,29,44,45,76]. Limited access and lack of standardization have prevented general clinical use of the DLST and consequently TTK scale applications outside Japan[29]; this may be due to methodological difficulties with false positive and false negative cases in the DLST[25,75]. For clinicians, the TTK scale cannot replace the CIOMS scale[25].

The DILIN method provided by the DILIN group requires an expert panel[3,6,11,24,44,45,49,50,77,78], in contrast to the CIOMS scale[21,24]. Consequently, the DILIN method is of limited availability to physicians in need of early results for therapeutic decisions[24]. In particular, the DILIN method is not an appropriate substitute for the CIOMS scale, nor are other expert panel based approaches[24]. This includes the novel Causality Assessment Tool (CAT) specifically designed for herbs and dietary supplements (HDS), which was presented as an abstract[15]. As opposed to CIOMS based results with transparent data presentation (Table 7)[12,30,32,36-39,47,48,71], publications based on the DILIN method lack transparency for individual cases regarding assessed and scored items since only final causality levels are published without details and thereby open for discussions, not allowing valid conclusions[3,6,11,49,50,77,78]. The DILIN method also lacks data on specificity, sensitivity and predictive values, as an expert opinion based method no items can be validated. Individual weighing and scoring of items remain undisclosed and undiscussed, hampering thorough analysis of assessment results by the DILIN method.

Liver unspecific methods

In contrast to the liver specific core elements of the original and updated CIOMS scale (Tables 1 and 2)[4,21-24], numerous causality algorithms are liver unspecific[4,24,76,79,80], including the Naranjo scale[81], the World Health Organization (WHO) global introspection method as the WHO method in short[82], and the KL method of Karg and Lasagna[83]. Particularly intensive discussions focused on the Naranjo scale[4,24,25,84-87], the WHO method[4,24,84,87], and the KL method[24,25]. All these methods are obsolete for causality assessment of assumed hepatotoxicity as they lack liver specificity and do not consider hepatotoxicity characteristics.

WEAKNESSES

Retrospective use

Retrospective analysis of case data is problematic and may require some assistance evaluating the CIOMS items[14,44,45]; unselected and sometimes undefined, low quality data have to be adapted into a structured algorithm like the CIOMS scale. Therefore, physicians should prospectively use the CIOMS scale, which then may provide complete case data (Table 7)[30].

Dechallenge criteria

Missing ALT dechallenge data are factored as 0 points given (Table 1); this condition has been interpreted as a limitation of the CIOMS scale[14]. Retrospective studies commonly lack dechallenge results[6,12,32,34-39] which are included in prospective evaluations (Table 7)[30]. CIOMS performs inaccurately in acute liver failure and liver transplantation if liver values are not available within 30 d after cessation of the incriminated drug or herb. Under these circumstances, 0 but not negative points are credited due to lacking ALT data (Tables 1 and 2).

Risk factors

The CIOMS scale includes only the risk factors of alcohol and age $\geqslant$ 55 years[21]. Diabetes, metabolic syndrome, sex, ethnicity and body mass index[14], as well as genetic predisposition[29], are also proposed as potential risk factors; the lack of inclusion in the CIOMS scale has been considered as a limitation[14,29]. However, these factors have not been validated as risk factors; their inclusion into the CIOMS scale requires evidence as independent contributors and a subsequent new validation.

Alternative causes

It may be argued that rare alternative causes were not listed in the CIOMS scale (Tables 1 and 2) but this shortcoming was compensated for by the checklist for numerous rare liver diseases as a reminder for the clinician (Table 3)[24].

Previous information on hepatotoxicity of drug/herb

Safety labels are available for both synthetic and herbal drugs but rarely for other herbal products. This shortcoming of the CIOMS scale may be compensated by a thorough search for prior publications of hepatotoxicity by herbal products; published reports provide an even higher scoring than information obtained only from safety labels.

CONCLUSION

The major strength of the CIOMS is its potential as a standard scale for DILI and HILI causality assessment by attending physicians, regulatory agencies, expert panels and the scientific community. Other advantages include its liver specificity and its validation for hepatotoxicity cases, with excellent sensitivity, specificity and predictive validity based on results obtained from cases with a positive reexposure test. This scale will allow the physician treating patients with suspected DILI and HILI an early preliminary result of the likelihood, facilitates timely and prospective collection of all relevant data required for a subsequent valid causality assessment, does not require an expert panel, and has the option of subsequent refinement by regulatory agencies, expert panels and the scientific community. With the CIOMS scale, an identical causality assessment algorithm can used by all evaluating parties, which facilitates the overall procedure of causality association. Minor weaknesses of the CIOMS scale include the limited exclusion of alternative causes and the handling of poor case data in

retrospectively rather than prospectively assessed cases.

REFERENCES

1 **Aithal GP**, Rawlins MD, Day CP. Accuracy of hepatic adverse drug reaction reporting in one English health region. *BMJ* 1999; **319**: 1541 [PMID: 10591713]
2 **Dalton HR**, Fellows HJ, Stableforth W, Joseph M, Thurairajah PH, Warshow U, Hazeldine S, Remnarace R, Ijaz S, Hussaini SH, Bendall RP. The role of hepatitis E virus testing in drug-induced liver injury. *Aliment Pharmacol Ther* 2007; **26**: 1429-1435 [PMID: 17850420 DOI: 10.1111/10.1111/j.1365-2036.2007.03504.x]
3 **Davern TJ**, Chalasani N, Fontana RJ, Hayashi PH, Protiva P, Kleiner DE, Engle RE, Nguyen H, Emerson SU, Purcell RH, Tillmann HL, Gu J, Serrano J, Hoofnagle JH. Acute hepatitis E infection accounts for some cases of suspected drug-induced liver injury. *Gastroenterology* 2011; **141**: 1665-1672.e1-9 [PMID: 21855518 DOI: 10.1053/j.gastro.2011.07.051]
4 **Teschke R**, Schwarzenboeck A, Eickhoff A, Frenzel C, Wolff A, Schulze J. Clinical and causality assessment in herbal hepatotoxicity. *Expert Opin Drug Saf* 2013; **12**: 339-366 [PMID: 23458441 DOI: 10.1517/14740338.2013.774371]
5 **Teschke R**, Schulze J, Schwarzenboeck A, Eickhoff A, Frenzel C. Herbal hepatotoxicity: suspected cases assessed for alternative causes. *Eur J Gastroenterol Hepatol* 2013; **25**: 1093-1098 [PMID: 23510966 DOI: 10.1097/MEG.0b013e3283603e89]
6 **Agarwal VK**, McHutchison JG, Hoofnagle JH. Important elements for the diagnosis of drug-induced liver injury. *Clin Gastroenterol Hepatol* 2010; **8**: 463-470 [PMID: 20170750 DOI: 10.1016/j.cgh.2010.02.008]
7 **Au JS**, Navarro VJ, Rossi S. Review article: Drug-induced liver injury--its pathophysiology and evolving diagnostic tools. *Aliment Pharmacol Ther* 2011; **34**: 11-20 [PMID: 21539586 DOI: 10.1111/j.1365-2036.2011.04674.x]
8 **Seeff LB**. Herbal hepatotoxicity. *Clin Liver Dis* 2007; **11**: 577-596, vii [PMID: 17723921]
9 **Navarro VJ**. Herbal and dietary supplement hepatotoxicity. *Semin Liver Dis* 2009; **29**: 373-382 [PMID: 19826971 DOI: 10.1055/s-0029-1240006]
10 **Bunchorntavakul C**, Reddy KR. Review article: herbal and dietary supplement hepatotoxicity. *Aliment Pharmacol Ther* 2013; **37**: 3-17 [PMID: 23121117 DOI: 10.1111/apt.12109]
11 **Chalasani N**, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, Rochon J. Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. *Gastroenterology* 2008; **135**: 1924-1934, 1934.e1-4 [PMID: 18955056 DOI: 10.1053/j.gastro.2008.09.011]
12 **Teschke R**, Schwarzenboeck A, Hennermann KH. Kava hepatotoxicity: a clinical survey and critical analysis of 26 suspected cases. *Eur J Gastroenterol Hepatol* 2008; **20**: 1182-1193 [PMID: 18989142 DOI: 10.1097/MEG.0b013e3283036768]
13 **Liss G**, Lewis JH. Drug-induced liver injury: what was new in 2008? *Expert Opin Drug Metab Toxicol* 2009; **5**: 843-860 [PMID: 19505188 DOI: 10.1517/17425250903018904]
14 **Aithal GP**, Watkins PB, Andrade RJ, Larrey D, Molokhia M, Takikawa H, Hunt CM, Wilke RA, Avigan M, Kaplowitz N, Bjornsson E, Daly AK. Case definition and phenotype standardization in drug-induced liver injury. *Clin Pharmacol Ther* 2011; **89**: 806-815 [PMID: 21544079 DOI: 10.1038/clpt.2011.58]
15 **Navarro VJ**, Barnhart HX, Bonkovsky HL, Reddy KR, Seeff L, Serrano J, Talwalkar JA, Vega M, Vuppalanchi R. Diagnosing hepatotoxicity attributable to herbal and dietary supplements: test- retest reliability of novel causality assessment tool. *J Hepatol* 2012; **55** (Suppl 2): S536 [DOI: 10.1016/S0168-8278(12)61375-0]
16 **Björnsson E**, Jacobsen EI, Kalaitzakis E. Hepatotoxicity associated with statins: reports of idiosyncratic liver injury postmarketing. *J Hepatol* 2012; **56**: 374-380 [PMID: 21889469 DOI: 10.1016/j.jhep.2011.07.023]
17 **Teschke R**, Frenzel C, Glass X, Schulze J, Eickhoff A. Greater Celandine hepatotoxicity: a clinical review. *Ann Hepatol* 2012; **11**: 838-848 [PMID: 23109446]
18 **Chalasani N**, Björnsson E. Risk factors for idiosyncratic drug-induced liver injury. *Gastroenterology* 2010; **138**: 2246-2259 [PMID: 20394749 DOI: 10.1053/j.gastro.2010.04.001]
19 **Larrey D**, Faure S. Herbal medicine hepatotoxicity: a new step with development of specific biomarkers. *J Hepatol* 2011; **54**: 599-601 [PMID: 21167851 DOI: 10.1016/j.jhep2010.12.003]
20 **Grant LM**, Rockey DC. Drug-induced liver injury. *Curr Opin Gastroenterol* 2012; **28**: 198-202 [PMID: 22450893 DOI: 10.1097/MOG.0b013e3283528b5d]
21 **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* 1993; **46**: 1323-1330 [PMID: 8229110]
22 **Benichou C**, Danan G, Flahault A. Causality assessment of adverse reactions to drugs--II. An original model for validation of drug causality assessment methods: case reports with positive rechallenge. *J Clin Epidemiol* 1993; **46**: 1331-1336 [PMID: 8229111]
23 **Teschke R**, Schwarzenboeck A, Hennermann KH. Causality assessment in hepatotoxicity by drugs and dietary supplements. *Br J Clin Pharmacol* 2008; **66**: 758-766 [PMID: 19032721 DOI: 10.1111/j.1365-2125.2008.03264.x]
24 **Teschke R**, Frenzel C, Schulze J, Eickhoff A. Herbal hepatotoxicity: challenges and pitfalls of causality assessment methods. *World J Gastroenterol* 2013; **19**: 2864-2882 [PMID: 23704820 DOI: 10.3748/wjg.v19.i19.2864]
25 **Teschke R**, Eickhoff A, Schulze J. Drug and herb induced liver injury in clinical and translational hepatology: Causality assessment methods, quo vadis? *J Clin Translat Hepatol* 2013; **1**: 59-74 [DOI: 10.14218/JCTH.2013.D002X]
26 **Danan G**. Causality assessment of drug-induced liver injury. Hepatology Working Group. *J Hepatol* 1988; **7**: 132-136 [PMID: 3053889]
27 **Bénichou C**. Criteria of drug-induced liver disorders. Report of an international consensus meeting. *J Hepatol* 1990; **11**: 272-276 [PMID: 2254635]
28 **Tajiri K**, Shimizu Y. Practical guidelines for diagnosis and early management of drug-induced liver injury. *World J Gastroenterol* 2008; **14**: 6774-6785 [PMID: 19058303 DOI: 10.3748/wig.14.6774]
29 **García-Cortés M**, Stephens C, Lucena MI, Fernández-Castañer A, Andrade RJ. Causality assessment methods in drug induced liver injury: strengths and weaknesses. *J Hepatol* 2011; **55**: 683-691 [PMID: 21349301 DOI: 10.1016/j.jhep.2011.02.007]
30 **Teschke R**, Bahre R. Severe hepatotoxicity by Indian Ayurvedic herbal products: a structured causality assessment. *Ann Hepatol* 2009; **8**: 258-266 [PMID: 19841509]
31 **Avelar-Escobar G**, Méndez-Navarro J, Ortiz-Olvera NX, Castellanos G, Ramos R, Gallardo-Cabrera VE, Vargas-Alemán Jde J, Díaz de León O, Rodríguez EV, Dehesa-Violante M. Hepatotoxicity associated with dietary energy supplements: use and abuse by young athletes. *Ann Hepatol* 2012; **11**: 564-569 [PMID: 22700641]
32 **Teschke R**, Glass X, Schulze J, Eickhoff A. Suspected Greater Celandine hepatotoxicity: liver-specific causality evaluation of published case reports from Europe. *Eur J Gastroenterol Hepatol* 2012; **24**: 270-280 [PMID: 22189691 DOI: 10.1097/MEG.0b013e32834f993f]
33 **Teschke R**, Frenzel C, Schulze J, Schwarzenboeck A, Eickhoff A. Herbalife hepatotoxicity: Evaluation of cases with positive reexposure tests. *World J Hepatol* 2013; **5**: 353-363 [PMID: 23898368 DOI: 10.4254/wjh.v5.i7.535]
34 **Teschke R**. Kava hepatotoxicity--a clinical review. *Ann Hepatol* 2010; **9**: 251-265 [PMID: 20720265]
35 **Teschke R**, Schwarzenboeck A, Schmidt-Taenzer W, Wolff

A, Hennermann KH. Herb induced liver injury presumably caused by black cohosh: a survey of initially purported cases and herbal quality specifications. *Ann Hepatol* 2011; **10**: 249-259 [PMID: 21677326]
36 **Teschke R**, Schmidt-Taenzer W, Wolff A. Spontaneous reports of assumed herbal hepatotoxicity by black cohosh: is the liver-unspecific Naranjo scale precise enough to ascertain causality? *Pharmacoepidemiol Drug Saf* 2011; **20**: 567-582 [PMID: 21702069 DOI: 10.1002/pds.2127]
37 **Teschke R**, Glass X, Schulze J. Herbal hepatotoxicity by Greater Celandine (Chelidonium majus): causality assessment of 22 spontaneous reports. *Regul Toxicol Pharmacol* 2011; **61**: 282-291 [PMID: 21893153 DOI: 10.1016/j.yrtph.2011.08.008]
38 **Teschke R**, Frenzel C, Schulze J, Eickhoff A. Spontaneous reports of primarily suspected herbal hepatotoxicity by Pelargonium sidoides: was causality adequately ascertained? *Regul Toxicol Pharmacol* 2012; **63**: 1-9 [PMID: 22381150 DOI: 10.1016/j.yrtph.2012.02.009]
39 **Teschke R**, Frenzel C, Wolff A, Herzog J, Glass X, Schulze J, Eickhoff A. Initially purported hepatotoxicity by Pelargonium sidoides: the dilemma of pharmacovigilance and proposals for improvement. *Ann Hepatol* 2012; **11**: 500-512 [PMID: 22700632]
40 **World Health Organization**. Assessments of the risk of hepatotoxicity with kava products. Geneva: WHO Document Production Services, 2007
41 **Estes JD**, Stolpman D, Olyaei A, Corless CL, Ham JM, Schwartz JM, Orloff SL. High prevalence of potentially hepatotoxic herbal supplement use in patients with fulminant hepatic failure. *Arch Surg* 2003; **138**: 852-858 [PMID: 12912743]
42 **Mahady GB**, Low Dog T, Barrett ML, Chavez ML, Gardiner P, Ko R, Marles RJ, Pellicore LS, Giancaspro GI, Sarma DN. United States Pharmacopeia review of the black cohosh case reports of hepatotoxicity. *Menopause* 2008; **15**: 628-638 [PMID: 18340277 DOI: 10.1097/gme.0b013e3181605bf]
43 **Sarma DN**, Barrett ML, Chavez ML, Gardiner P, Ko R, Mahady GB, Marles RJ, Pellicore LS, Giancaspro GI, Low Dog T. Safety of green tea extracts : a systematic review by the US Pharmacopeia. *Drug Saf* 2008; **31**: 469-484 [PMID: 18484782]
44 National Institutes of Health (NIH): NIH launches free database of drugs associated with liver injury. October 12, 2012 news release. Available from: URL: http://www.nih.gov/news/health/oct2012/niddk-12.htm
45 National Institutes of Health (NIH) and LiverTox: Drug record. Herbals and dietary supplements. February 20, 2012 last updated. Available from: URL: http://www.livertox.nih.gov/Herbals_and_Dietary_Supplements.htm
46 **Teschke R**, Genthner A, Wolff A. Kava hepatotoxicity: comparison of aqueous, ethanolic, acetonic kava extracts and kava-herbs mixtures. *J Ethnopharmacol* 2009; **123**: 378-384 [PMID: 19501269 DOI: 10.1016/j.jep.2009.03.038]
47 **Teschke R**, Schwarzenboeck A. Suspected hepatotoxicity by Cimicifugae racemosae rhizoma (black cohosh, root): critical analysis and structured causality assessment. *Phytomedicine* 2009; **16**: 72-84 [PMID: 19010650 DOI: 10.1016/j.phymed.2008.09.009]
48 **Teschke R**, Bahre R, Fuchs J, Wolff A. Black cohosh hepatotoxicity: quantitative causality evaluation in nine suspected cases. *Menopause* 2009; **16**: 956-965 [PMID: 19339903 DOI: 10.1097/GME.0b013e31819d3904]
49 **Rochon J**, Protiva P, Seeff LB, Fontana RJ, Liangpunsakul S, Watkins PB, Davern T, McHutchison JG. Reliability of the Roussel Uclaf Causality Assessment Method for assessing causality in drug-induced liver injury. *Hepatology* 2008; **48**: 1175-1183 [PMID: 18798340 DOI: 10.1002/hep.22442]
50 **Rockey DC**, Seeff LB, Rochon J, Freston J, Chalasani N, Bonacini M, Fontana RJ, Hayashi PH. Causality assessment in drug-induced liver injury using a structured expert opinion process: comparison to the Roussel-Uclaf causality assessment method. *Hepatology* 2010; **51**: 2117-2126 [PMID: 20512999 DOI: 10.1002/hep.23577]
51 **Watanabe M**, Shibuya A. Validity study of a new diagnostic scale for drug-induced liver injury in Japan-comparison with two previous scales. *Hepatol Res* 2004; **30**: 148-154 [PMID: 15588780 DOI: 10.1016/j.hepres.2004.08.005]
52 **Björnsson E**, Olsson R. Outcome and prognostic markers in severe drug-induced liver disease. *Hepatology* 2005; **42**: 481-489 [PMID: 16025496]
53 **Teschke R**, Wolff A, Frenzel C, Schulze J, Eickhoff A. Herbal hepatotoxicity: a tabular compilation of reported cases. *Liver Int* 2012; **32**: 1543-1556 [PMID: 22928722]
54 EMA (European Medicines Agency): Assessment of case reports connected to herbal medicinal products containing cimicifugae racemosae rhizoma (black cohosh, root). Issued May 8, 2007. Available from: URL: http://www.ema.europa.eu/docs/en_GB/document_library/Herbal_HMPC_assessment_report/2010/02/WC500074167.pdf
55 **Miljkovic MM**, Dobric S, Dragojevic-Simic V. Consistency between causality assessments obtained with two scales and their agreement with clinical judgments in hepatotoxicity. *Pharmacoepidemiol Drug Saf* 2011; **20**: 272-285 [PMID: 21351309 DOI: 10.1002/pds.2081]
56 **Miljkovic MM**, Dobric S, Dragojevic-Simic V. Accuracy and reproducibility of two scales in causality assessment of unexpected hepatotoxicity. *J Clin Pharm Ther* 2012; **37**: 196-203 [PMID: 21718339 DOI: 10.1111/j.1365-2710.2011.01282.x]
57 **Chau TN**, Cheung WI, Ngan T, Lin J, Lee KWS, Poon WT, Leung VKS, Mak T, Tse ML, and the Hong Kong Herb-Induced Liver Injury Network (HK-HILIN). Causality assessment of herb- induced liver injury using multidisciplinary approach and the Roussel Uclaf Causality assessment Method (RUCAM). *Clin Toxicol* 2011; **49**: 34-39 [10.3109/15563650.2010.537662]
58 **BfArM (Bundesinstitut für Arzneimittel und Medizinprodukte,** Bonn. Federal Institute for Drugs and Medicinal Products in Germany). Rejection of Drug Risks, Step II. As related to: Kava-Kava (Piper methysticum)-containing, and kavain-containing drugs, including homeopathic preparations with a final concentration up to, and including D4. June 14, 2002. Available from: URL: http://www.spc.int/cis/documents/02_0714_BfArM_Kava_Removal.pdf
59 **Denham A**, McIntyre M, Whitehouse J. Kava--the unfolding story: report on a work-in-progress. *J Altern Complement Med* 2002; **8**: 237-263 [PMID: 12165183 DOI: 10.1089/10755530260127943]
60 **Teschke R**, Gaus W, Loew D. Kava extracts: safety and risks including rare hepatotoxicity. *Phytomedicine* 2003; **10**: 440-446 [PMID: 12834011 DOI: 10.1078/0944-7113-00314]
61 **Stickel F**, Baumüller HM, Seitz K, Vasilakis D, Seitz G, Seitz HK, Schuppan D. Hepatitis induced by Kava (Piper methysticum rhizoma). *J Hepatol* 2003; **39**: 62-67 [PMID: 12821045 DOI: 10.1016/S0168-8278(03)00175-2]
62 **Schmidt M**, Morgan M, Bone K, McMillan J. Kava: a risk-benefit assessment. In: Mills M, Bone K. The essential guide to herbal safety. St. Louis: Elsevier Churchill Livingstone, 2005: 155-221
63 **Bundesinstitut für Arzneimittel und Medizinprodukte.** Bekanntmachung. Abwehr von Gefahren durch Arzneimittel, Stufe II, Anhörung: Schöllkraut-haltige Arzneimittel zur innerlichen Anwendung. May 6, 2005. Available from: URL: http://www.bfarm.de/cae/servlet/contentblob/1014620/publicationFile/66198/schoellkraut- anhoerung_050505.pdf
64 **Elinav E**, Pinsker G, Safadi R, Pappo O, Bromberg M, Anis E, Keinan-Boker L, Broide E, Ackerman Z, Kaluski DN, Lev B, Shouval D. Association between consumption of Herbalife nutritional supplements and acute hepatotoxicity. *J Hepatol* 2007; **47**: 514-520 [PMID: 17692424]
65 **Schoepfer AM**, Engel A, Fattinger K, Marbet UA, Criblez D, Reichen J, Zimmermann A, Oneta CM. Herbal does not mean innocuous: ten cases of severe hepatotoxicity associ-

ated with dietary supplements from Herbalife products. *J Hepatol* 2007; **47**: 521-526 [PMID: 17692989]
66 **Fong TL**, Klontz KC, Canas-Coto A, Casper SJ, Durazo FA, Davern TJ, Hayashi P, Lee WM, Seeff LB. Hepatotoxicity due to hydroxycut: a case series. *Am J Gastroenterol* 2010; **105**: 1561-1566 [PMID: 20104221 DOI: 10.1038/ajg.2010.5]
67 **Manso G**, López-Rivas L, Salgueiro ME, Duque JM, Jimeno FJ, Andrade RJ, Lucena MI. Continuous reporting of new cases in Spain supports the relationship between Herbalife ® products and liver injury. *Pharmacoepidemiol Drug Saf* 2011; **20**: 1080-1087 [PMID: 21751292 DOI: 10.1002/pds.2180]
68 **Maria VA**, Victorino RM. Development and validation of a clinical scale for the diagnosis of drug-induced hepatitis. *Hepatology* 1997; **26**: 664-669 [PMID: 9303497 DOI: 10.1002/hep.510260319]
69 **Kaplowitz N**. Causality assessment versus guilt-by-association in drug hepatotoxicity. *Hepatology* 2001; **33**: 308-310 [PMID: 11124850]
70 **Lucena MI**, Camargo R, Andrade RJ, Perez-Sanchez CJ, Sanchez De La Cuesta F. Comparison of two clinical scales for causality assessment in hepatotoxicity. *Hepatology* 2001; **33**: 123-130 [PMID: 11124828 DOI: 10.1053/jhep.2001.20645]
71 **Teschke R**, Fuchs J, Bahre R, Genthner A, Wolff A. Kava hepatotoxicity: comparative study of two structured quantitative methods for causality assessment. *J Clin Pharm Ther* 2010; **35**: 545-563 [PMID: 20831679 DOI: 10.1111/j.1365-2710.2009.01131.x]
72 **Aithal PG**, Day CP. The natural history of histologically proved drug induced liver disease. *Gut* 1999; **44**: 731-735 [PMID: 10205214 DOI: 10.1136/gut.44.5.731]
73 **Aithal GP**, Rawlins MD, Day CP. Clinical diagnostic scale: a useful tool in the evaluation of suspected hepatotoxic adverse drug reactions. *J Hepatol* 2000; **33**: 949-952 [PMID: 11131457 DOI: 10.1016/S0168-8278(00)80127-0]
74 **Takikawa H**, Takamori Y, Kumagi T, Onji M, Watanabe M, Shibuya A, Hisamochi A, Kumashiro R, Ito T, Mitsumoto Y, Nakamura A, Sakaguchi T. Assessment of 287 Japanese cases of drug induced liver injury by the diagnostic scale of the International Consensus Meeting. *Hepatol Res* 2003; **27**: 192-195 [PMID: 14585395 DOI: 10.1016/S1386-6346(03)00232-8]
75 **Takikawa H**. Recent status of drug-induced liver injury and its problems in Japan. *Jap Med Ass J* 2010; **53**: 243-247
76 **Agbabiaka TB**, Savović J, Ernst E. Methods for causality assessment of adverse drug reactions: a systematic review. *Drug Saf* 2008; **31**: 21-37 [PMID: 18095744 DOI: 10.2165/00002018-200831010-00003]
77 **Fontana RJ**, Watkins PB, Bonkovsky HL, Chalasani N, Davern T, Serrano J, Rochon J. Drug-Induced Liver Injury Network (DILIN) prospective study: rationale, design and conduct. *Drug Saf* 2009; **32**: 55-68 [PMID: 19132805 DOI: 10.2165/00002018-200932010-00005]
78 **Fontana RJ**, Seeff LB, Andrade RJ, Björnsson E, Day CP, Serrano J, Hoofnagle JH. Standardization of nomenclature and causality assessment in drug-induced liver injury: summary of a clinical research workshop. *Hepatology* 2010; **52**: 730-742 [PMID: 20564754 DOI: 10.1002/hep.23696]
79 **Macedo AF**, Marques FB, Ribeiro CF, Teixeira F. Causality assessment of adverse drug reactions: comparison of the results obtained from published decisional algorithms and from the evaluations of an expert panel, according to different levels of imputability. *J Clin Pharm Ther* 2003; **28**: 137-143 [PMID: 12713611 DOI: 10.1046/j.1365-2710.2003.00475.x]
80 **Aronson JK**. Adverse drug reactions: History, terminology, classification, causality, frequency, preventability. In: Talbot J, Aronson JK. Stephens' Detection and Evaluation of Adverse Drug Reactions: Principles and Practice, 6th ed. Chichester: John Wiley & Sons, Ltd, 2011
81 **Naranjo CA**, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, Janecek E, Domecq C, Greenblatt DJ. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981; **30**: 239-245 [PMID: 7249508 DOI: 10.1038/clpt.1981.154]
82 **World Health Organization**. The use of the WHO-UMC system for standardised case causality assessment. WHO Collaborating Centre for International Drug Monitoring (Uppsala Monitoring Centre, UMC), Database 2000. Available from: URL: http://who-umc.org/Graphics/24734.pdf
83 **Karch FE**, Lasagna L. Toward the operational identification of adverse drug reactions. *Clin Pharmacol Ther* 1977; **21**: 247-254 [PMID: 837643]
84 **Teschke R**, Wolff A. Regulatory causality evaluation methods applied in kava hepatotoxicity: are they appropriate? *Regul Toxicol Pharmacol* 2011; **59**: 1-7 [PMID: 20854865 DOI: 10.1016/j.yrtph.2010.09.006]
85 **Teschke R**, Schulze J. Suspected herbal hepatotoxicity: requirements for appropriate causality assessment by the US Pharmacopeia. *Drug Saf* 2012; **35**: 1091-1097 [PMID: 22897137]
86 **García-Cortés M**, Lucena MI, Pachkoria K, Borraz Y, Hidalgo R, Andrade RJ. Evaluation of naranjo adverse drug reactions probability scale in causality assessment of drug-induced liver injury. *Aliment Pharmacol Ther* 2008; **27**: 780-789 [PMID: 18284654 DOI: 10.1111/j.1365-2036.2008.03655.x]
87 **Teschke R**, Eickhoff A, Wolff A, Frenzel C, Schulze J. Herbal hepatotoxicity and WHO global introspection method. *Ann Hepatol* 2013; **12**: 11-21 [PMID: 23293189]

P- Reviewers: Castiella A, Shi Q, Skok P
S- Editor: Zhai HH **L- Editor**: Roemmele A **E- Editor**: Liu XM

百世登
Baishideng®

Published by **Baishideng Publishing Group Co., Limited**
Flat C, 23/F., Lucky Plaza,
315-321 Lockhart Road, Wan Chai, Hong Kong, China
Fax: +852-65557188
Telephone: +852-31779906
E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com