PRO-EURO DILI NETWORK
Prospective European Drug-induced Liver Injury Network

1st TRAINING COURSE, ACTION COST 17-112 PRO EURO DILI NET

Causality assessment scales: strengths and weaknesses

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SPANISH DILI REGISTRY

ciberehd

WHY IS IMPORTANT TO MAKE A CORRECT AND EARLY DIAGNOSIS OF DILI?

The treatment of DILI is based on dechallenge of the suspected culprit/s drug/s

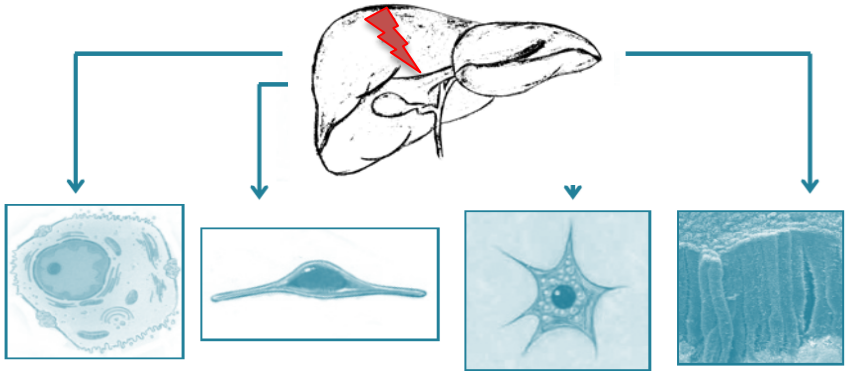
- Decrease the risk of progression to acute liver failure
- Decrease progression to chronic liver injury.
- Avoid rechallenge.
- Avoid delay of correct diagnosis if no DILI.
- Withdrawal time reduction of new marketed hepatotoxic drugs.

Rare disease

No definitive diagnostic test or biomarker

DILI DIAGNOSIS CHALLENGES

Different types of liver injury



Rare disease

No definitive diagnostic test or biomarker

DILI DIAGNOSIS CHALLENGES

Different types of liver injury

CAUSALITY ASSESSMENT

CAUSALITY ASSESSMENT

Evaluation of the likelihood that a particular drug or treatment is the cause of an observed adverse event.

PHYSICIAN AWARENES

- Compatible temporal relationship
- Exclusion of other causes of liver injury.
- Objective weighting of the circumstantial evidence.

CAUSALITY ASSESSMENT

Liver injury

Suspicion of DILI

Retrieve pharmaceutical history

Identify exposure to potential DILI agent

CLINICAL ASSESSMENT

CAUSALITY ASSESSMENT METHODS

eDILI

LiverTox
Clinical and Research Information on Drug-Induced Liver Injury
www.livertox.nih.gov

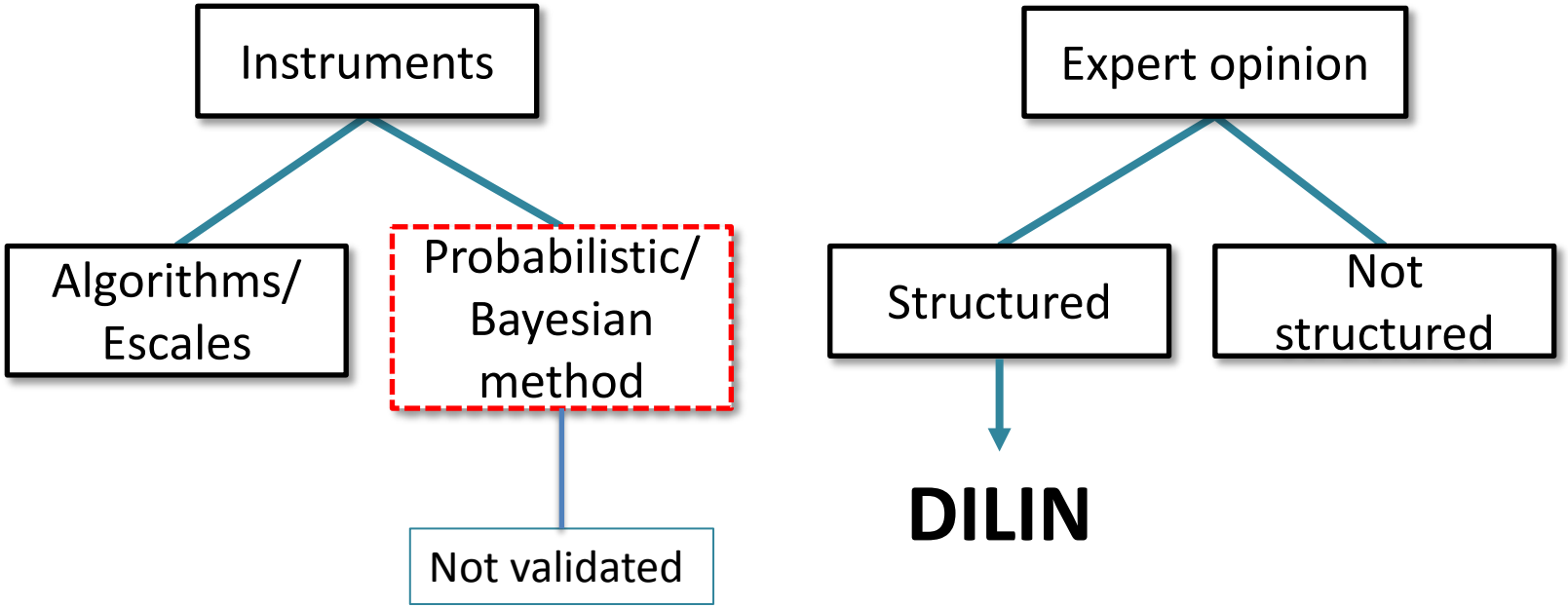
García-Cortés M, et al. J Hepatology 2011.

CAUSALITY ASSESSMENT METHODS

Structured and objective process of evaluation of suspected DILI cases.

- Allow for an uniform approach of evaluation of DILI.
- Qualities required: **VALIDITY AND REPRODUCIBILITY**
- Common criteria

CAUSALITY ASSESSMENT METHODS



CAUSALITY ASSESMENT SCALES AND ALGORITHMS

GENERAL OR UNSPECIFIC METHODS:

- Karch y Lasagna (1977)
- Kramer (1979)
- **Naranjo** (1981)
- Jones (1982): FDA.
- The French method: Begaud (1984).
- Arimone (2006)
- WHO-Uppsala Monitoring Center (WHO-UMC) scale.

SPECIFIC METHODS FOR DILI ASSESSMENT:

- Striker (1992)
- **CIOMS/RUCAM** (1993)
- **Maria & Victorino or CDS** (1997)
- Digestive Disease Week Japan (DDW-J) scale (2003)
- Updated RUCAM (2016)

NARANJO ADR PROBABILITY SCALE

Naranjo Adverse Drug Reaction Probability Scale				
Question	Yes	No	Do Not Know	Score
1. Are there previous *conclusive* reports on this reaction?	+1	0	0	
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	
3. Did the adverse reaction improve when the drug was discontinued or a *specific* antagonist was administered?	+1	0	0	
4. Did the adverse event reappear when the drug was re-administered?	+2	-1	0	
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	
6. Did the reaction reappear when a placebo was given?	-1	+1	0	
7. Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	+1	0	0	
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	
9. Did the patient have a similar reaction to the same or similar drugs in *any* previous exposure?	+1	0	0	
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	

Total Score ≥9 **Definite.**
Total Score 5 to 8 **Probable.**
Total Score 1 to 4 **Possible.**
Total Score ≤0 **Doubtful.**

Naranjo CA, et al. Clin Pharmacol Ther 1981.

Council for International Organizations of Medical Sciences

CIOMS/RUCAM SCALE

	Type of liver injury				Score
	Hepatocellular		Cholestatic/mixed		
Time of onset of the event:	First treat	2nd treat	First treat	2nd treat	
From drug intake until reaction onset	5-90 days	1-15 days	5-90 days	1-90 days	+2
	<5 or >90 days	>15 days	<5 or >90 days	>90 days	+1
From drug withdrawal until reaction onset	< or = 15 days	< or = 15 days	< or = 30 days	< or = 30 days	+1
Course of the reaction	>50% improvement 8 days.				+3
	>50% improvement 30 days		>50% improvement 180 d		+2
			<50% improvement 180 d		+1
	Lack of information or no improvement		Lack of information or no improvement		0
	Worsening or <50% improvement 30 days				-1
Risk Factors	Alcohol		Alcohol or pregnancy		+1
	Age > or = 55 years		Age > or = 55 years		+1
Concomitant therapy					-3 to 0
Exclusion of non-drug related causes					-3 to 2
Previous information on hepatotoxicity					0 to +2
Re-challenge					-2 to +3

Results: > 8 points definite; 6-8 points probable; 3-5 points possible; 1-2 points unlikely; < 0 points excluded

Danan J, et al. Clin Epidemiol 1993

CIOMS/RUCAM SCALE

- CIOMS/RUCAM was initially validated using a cohort of 49 published DILI with positive re-challenge as well as in 28 non-DILI controls.
  - sensitivity 86%
  - specificity 89%
  - positive predictive value 93%
  - negative predictive value 78%

- The reproducibility of the scale was evaluated by the application of the method to 50 cases of suspected DILI by four experts.
  - Agreement 2 experts: 99%
  - Agreement 3 experts: 74%
  - Agreement 4 experts: 37 %

Benichou C. J Hepatol 1990.
Bénichou C, et al. J Clin Epidemiol 1993.

CIOMS/RUCAM SCALE
Strenghts and Weaknesses

STRENGHTS	LIMITATIONS
Improve validity	Ambiguous instructions
	Definition of type of injury
Improve Objectivity	Unclear criteria for competing cause/drug
	Alcohol use
More Reproducibility	Arbitrary weighting of factors
	Overweighting of rechallenge
Excellent teaching tool	Questionable risk factors
	Inappropriate penalty delay onset
Checklist	Excessive penalty for competing hepatotoxic drug
	Variability among raters

MARIA & VICTORINO or CLINICAL DIAGNOSTIC SCALE

Chronological criteria	
From drug intake until onset event	
4 days to 8 weeks	+3
Less than 4 days or more than 8 weeks	+1
From drug withdrawal until onset event	
0 to 7 days	+3
8 to 15 days	0
More than 15 days	-3
Normalization of laboratory values after drug withdrawal	
Less than 6 mo (cholestatic) or 2 mo (hepatocellular)	+3
More than 6 mo or 2 mo	0
Exclusion of alternative causes for the ADR	
Complete exclusion	+3
Partial exclusion	0
Possible alternative causes	-1
Probable alternative causes	-3
Extrahepatic manifestations	
4 or more	+3
2 or 3	+2
1	+1
None	+0
PositiveRechallenge	+3
Known reaction	
Yes	+2
No (drug marketed for less than 5 years)	0
No (drug marketed for more than 5 years)	-3

Score > 17 definite
Score 14-17 probable
Score l0-13 possible
Score 6-9 unlikely
Score < 6 excluded

Maria VAJ, Victorino RMM. Hepatology 1997

MARIA & VICTORINO SCALE (CDS)

- Validation : real and fictitious cases of immunoallergic DILI and the opinion of a panel of experts as the gold standard
- Agreement 84 %.
- Less agreement in the item of exclusion of other causes of liver disease. Not specified.
- Worse reliability in cases with long latency period or chronicity.

Maria VAJ, Victorino RMM. Hepatology 1997

DIGESTIVE DISEASE WEEK-JAPAN (DDW-J)

DDW-J or TTK scale	
Axis	Score
Chronological criteria	
From drug intake until onset	+1 to +2
From drug withdrawal until onset	0 to +1
Course of the reaction	-2 to +3
Risk Factors	0 to +1
Exclusion of other causes	-3 to +2
Previous information	0 to +1
Rechallenge	0 to +3
Extrahepatic manifestations	0 to +1
Drug Lynphocyte stimulation test (DLST)	0 to +2
Results:	
> 4 points definite	
3-4 points probable	
< 3 points unlikely	

Takikawa H, Takamori, Y.; Kumagi, T. et al. Hepatol Res 2003.
Watanabe M, Shibuya A. Hepatol Res 2004.

DILIN EXPERT OPINION PROCESS

- Process where expert hepatologists evaluate prospectively collected clinical and laboratory data from cases of suspected DILI.
- The likelihood of an event being DILI is described using both a percentage figure and a descriptive legal terminology.

Label (Score)	Likelihood	Description
Definite (1)	>95%	The evidence for the drug causing the injury is beyond a reasonable doubt.
Highly likely (2)	75%-95%	The evidence for the drug causing the injury is clear and convincing but not definite.
Probable (3)	50%-74%	The preponderance of the evidence supports the link between the drug and the liver injury
Possible (4)	25%-49%	The evidence for the drug causing the injury is equivocal but present.
Unlikely (5)	<25%	There is evidence that an etiological factor other than a drug caused the injury.

Rockey et al. Hepatology 2010.

CAUSALITY ASSESSMENT METHODS
Comparative studies

CIOMS/RUCAM SCALE vs CDS

N: 228. (185 included and 30 excluded in the registry after the evaluation by 3 experts

CIOMS Scale	M&V					
	Excluded	Unlikely	Possible	Probable	Definite	Total
Excluded	21	2				23
Unlikely	4	3				7
Possible		8	1			9
Probable	1	30	43	16		90
Definite		5	40	53	1	99
Total	26	48	84	69	1	228

Absolute agreement 18%

K_w = 0.28

M&V:

Sensitivity: 37%

Specificity: 100%

Positive predictive value: 100%

Negative predictive value: 25%

	M&V		
	≥14	<14	Total
CIOMS ≥ 6	70	119	189
CIOMS < 6	0	39	39
Total	70	158	228

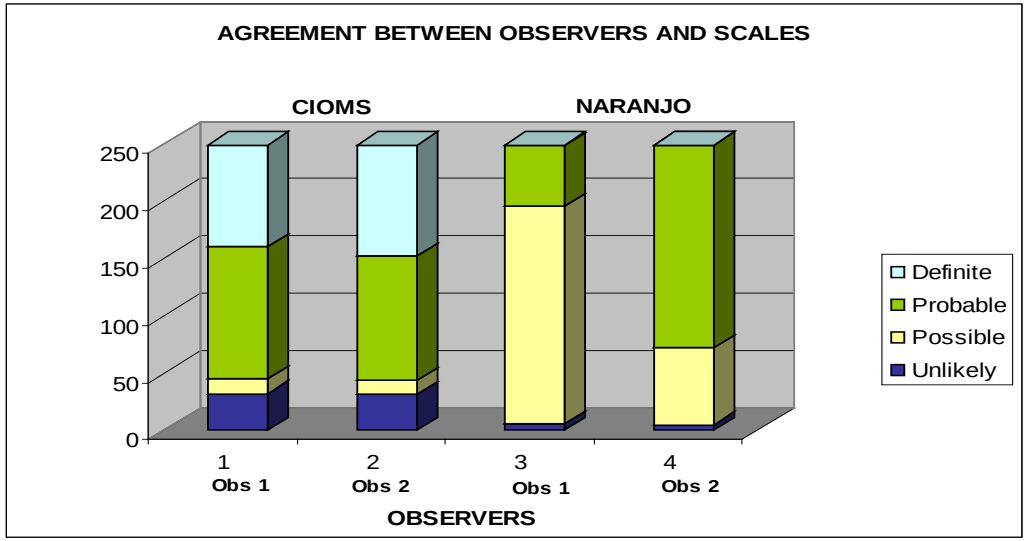
Lucena et al, Hepatology 2001

CIOMS/RUCAM SCALE vs CDS

- The scales correlate broadly with regards to the classification of events according to the likelihood of DILI.
- Discrepancies greater than one category level were seen in 31%.
- **Agreement was 6% in cases with features of cholestasis.**
- **No agreement in acute liver failure or death**.
- The CIOMS scale´s concordance with expert review was superior to that of the CDS.

Lucena M, et al. Hepatology 2001

CIOMS/RUCAM SCALE vs NARANJO ADR SCALE



Inter-scale agreement 24%

Weighted kappa 0.29

Inter-rater agreement 73%

K_w 0.87

Inter-rater agreement 44%

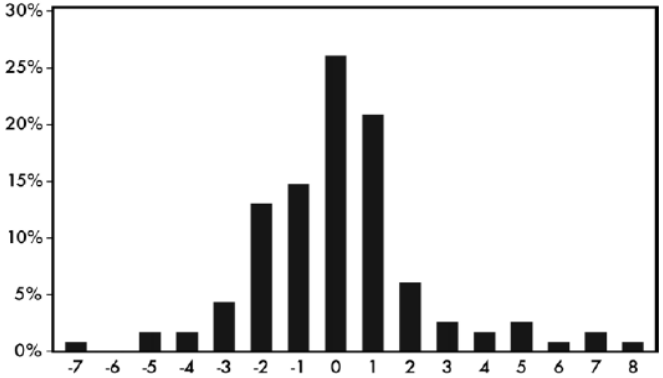
K_w 0.23

✓The majority of the scores yielded by the Naranjo scale were in the midrange with only one definite result and a low number of excluded cases showing a low discriminative power.

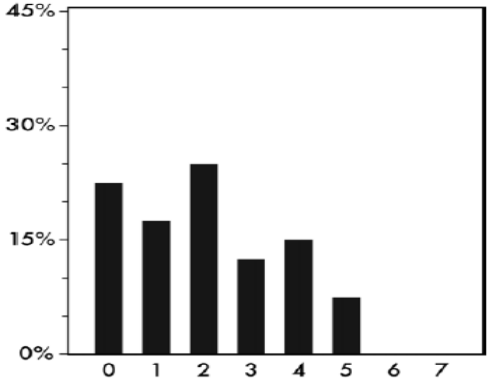
García-Cortés et al, Aliment Pharmacol Ther, 2008

CIOMS/RUCAM Reproducibility

- Test-retest complete agreement in 26% cases.
- Inter-rater reliability was 0.45



Intra-rater differences



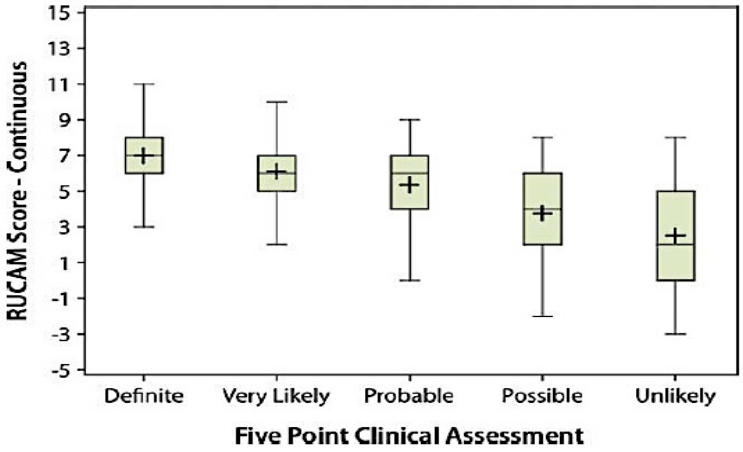
Inter-rater differences

Conclusions: "mediocre reliability" of RUCAM
Suggestions: modify the RUCAM, develope drug-specific instruments, or causality assessment based on expert opinion.

Rochon et al. Hepatology, 2008.

DILIN EXPERT OPINION PROCESS VS CIOMS/RUCAM

Correlation of the RUCAM and DILIN causality scores.



Rockey et al, Hepatology 2010.

- General relationship between the two scales **r 0.42**
- Considerable variability in the RUCAM score at each DILIN score.
- **Complete agreement**
  - **27% with expert opinion**
  - **19% with RUCAM.**

DILIN EXPERT OPINION PROCESS VS CIOMS/RUCAM

- The expert opinion process produced higher rates of inter-rater agreement and likelihood score.
- Substantial inter-observer variability persisted in both methods.
- The DILIN expert opinion process has not been externally validated.
- Expert opinion remains the main stay for causality assessment of new drugs with emerging adverse liver reactions that have not been fully Characterized.

Rockey et al. Hepatology 2010.
Regev A, et al. Drug saf 2014.

WHITCH METHOD IS BETTER?

CIOMS/RUCAM SCALE

- Demonstrated to be superior to the Naranjo scale.
- Better discriminative power and evaluations closer to those of specialists than the CDS.
- **Most commonly used causality assessment scale:**

  Majority of the studies use CIOMS scale for DILI case definition and inclusion criteria.

  American College of Gastroenterology Guidance recommends the CIOMS scale as a guide for the evaluation of patients with DILI.

DILIN EXPERT OPINION PROCESS

- Better for causality assessment of emerging DILI that have not been fully Characterized.

García-Cortés et al, Aliment Pharmacol Ther, 2008
Lucena et al, Hepatology 2001
Agarwal et al Clin Gastoenterol Hepatol 2010
Kaplowitz N. Hepatology 2001.
Chalasani NP, et al. Am J Gastroenterol.
Regev A, et al. Drug saf 2014.

STRENGTHS AND WEAKNESSES OF THE CAUSALITY ASSESSMENT SCALES

Strengths	Weaknesses
• Improve consistency and objectivity • More Specificity • More Reproducibility • Mechanisms to grade strength of final designation in broad categories • Excellent teaching tool • Checklist	• Complexity and time consuming • Do not provide certainty • Do not substitute “common sense” clinical judgement • Need cases with enough relevant information and follow up • Do not discriminate among concomitant drugs • Evaluation of fatal or atypical cases remain challenging

TAKE-HOME MESSAGES

- ✓ Causality assessment is an structured and objective process of evaluation of suspected DILI cases.
- ✓ The use of causality assessment methods adds consistency to the diagnostic process.
- ✓ The Naranjo ADR scale shows poor validity and reproducibility, and is an unspecific method for the evaluation of hepatotoxic reactions.
- ✓ The CIOMS/RUCAM is the most commonly used causality assessment scale in DILI as it has been proven to be superior to other scales.

TAKE-HOME MESSAGES

- ✓ CIOMS/RUCAM scale is a good checklist to remind physicians about which information is important in DILI diagnosis.
- ✓ The CIOMS/RUCAM scale has limitations: lack of clear instructions, limited information or atypical cases score less points, or questionable risk factors.
- ✓ Efforts are being made to improve the avaliable causality assessment methods.

Thank you for your attention

BREAKOUT GROUPS FOR ASSESSMENT OF DILI CASES

TIPS FOR CIOMS/RUCAM APPLICATION SUSPECTED DILI CASES

STEP ONE. CALCULATION OF THE R RATIO.

The initial step in the RUCAM assessment is to define whether the hepatic injury is "hepatocellular", "mixed", or "cholestatic."

The values used should be from the same day (or no more than 2 days apart) and should be those from the initial blood test results following onset of liver injury.

R = (ALT value ÷ ALT ULN) ÷ (Alk P value ÷ Alk P ULN)

- **R >5 hepatocellular**
- **R<2 cholestatic**
- **R 2-5 a mixed**

STEP TWO. CALCULATION OF THE RUCAM SCORE.

- **Incompatible: If the reaction begins before starting the medication or >15 days after stopping (hepatocellular), or >30 days after stopping (cholestatic), the injury should be considered unrelated and the RUCAM cannot be calculated.**

- **Unknown: When information is not avaliable to calculate date of onset ; insufficiently documented.**

	HEPATO CELLULAR TYPE	CHOLESTATIC OR MIXED TYPE	ASSESSMENT
TIME TO ONSET			
Incompatible	Reaction occured befote starting the drug or more than 15 days after stopping the drug (except for slowly metabolized drugs)	Reaction occurred before starting the drug or more than 30 days after stopping the drug (except for slowly metabolized drugs)	
Unknown	When Information is not available to calculate time to onset, then the case is		Insufficiently documented

CIOMS/RUCAM scale

TEMPORAL RELATIONSHIP

	Hepatocellular		Cholestatic or mixed		
	Initial treatment	Subsequent treatment	Initial treatment	Subsequent treatment	SCORE
-From the beginning of the drug					
Suggestive	5-90 days	1-15 days	5-90 days	1-90 days	+2
Compatible	<5 or >90 days	>15 days	<5 or > 90 days	> 90 days	+1
-From cessation of the drug					
Compatible	</= 15 days	</= 15 days	</= 30 days	</= 30 days	+1

COURSE	Difference between the peak of ALT (SGPT) and upper limits of normal values	Difference between the peak of A.P. (or TB) and upper limits of normal values	
Alter cessation of the drug			
Highly suggestive	Decrease >/= 50% within 8 days	Not applicable	+3
Suggestive	Decrease >/= 50% within 30 days	Decrease >/= 50% within 180 days	+2
Compatible	Not applicable	Decrease < 50% within 180 days	+1
Inconclusive	No information or decrease >/= 50%, after the 30th day	Persistence or Increase or no Information	0
Against the role of the drug	Decrease </= 50%, after the 30th days or recurrent increase	No situation. Not applicable	-2
If the drug is continued			
Inconclusive	All situations	All situations	0

CIOMS/RUCAM scale

RISK FACTORS

RISK FACTORS	Hepatocellular type Ethanol	Cholestatic or mixed type Ethanol or pregnancy	
Presence Absence			+1 0
Age of the patient >/= 55 years Age of the patient < 55 years			+1 0

CONCOMITANT DRUGS

CONCOMITANT DRUG(S)	
None or no information or concomitant drug with incompatible time to onset Concomitant drug with compatible or suggestive time to onset Concomitant drug known as hepatotoxin and with compatible or suggestive time to onset Concomitant drug with evidence for its role in this case (positive rechallange or validated test)	0 -1 -2 -3

CIOMS/RUCAM scale

EXCLUSION OF ALTERNATIVE CAUSES OF LIVER INJURY

SEARCH FOR NON DRUG CAUSES		
Group 1 (6 causes) Recent viral infection with HAV (IgM anti HAV) or HBV (IgM anti HBV) or HCV (anti HCV and non A- non B hepatitis); Biliary obstruction (ultrasonography); Alcoholism (AST/ALT >/= 2); Acute recent hypotension history (particularly if heart disease) Group II Complications of underlying disease; Clinical and/or biological Context suggesting CMV, EBV or Herpes virus infection	All causes - group I and II - reasonably ruled out The 6 causes of group I ruled out 4 or 5 causes of group I ruled out Less than 4 causes of group I ruled out Non drug cause highly probable	+2 +1 0 -2 -3

PREVIOUS INFORMATION ABOUT THE HEPATOTOXIC POTENTIAL OF THE DRUG

PREVIOUSE INFORMATION ON HEPATOTOXICITY OF THE DRUG	
Reaction labelled in the product characteristics Reaction published but unlabelled Reaction unknown	+2 +1 0

CIOMS/RUCAM scale

RECHALLENGE

	HEPATOCELLULAR	MIXED OR CHOLESTATIC	
RESPONSE TO READMINISTRATION			
Positive	Doubling of ALT with the drug alone	Doubling of AP (or TB) with the drug alone	+3
Compatible	Doubling of ALT with the drugs already given at the time of the 1st reaction	Doubling of AP (or TB) with the drug already given at the time of the 1st reaction	+1
Negative	Increase of ALT but less than N in the same conditions as for the first administration	Increase of AP (or TB) but less than N in the same conditions as for the fist administration	-2
Not done or not interpretable	Other situations	Other situations	0
		Total (add the encircled figures)	

The total score may be classified in 5 degrees:

SCORE <1 excluded; 1-2 unlikely; 3-5 possible; 6-8 probable, >8 highly probable