Causality Assessment: Which Is Best—Expert Opinion or RUCAM?

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There are no facts, only interpretations.

Friedrich Nietzche, 1886

Historical Perspectives of Causality Assessment

The late Hyman Zimmerman was always reticent to assign causality of hepatotoxicity to a medication unless other causes could be adequately excluded.[1] Indeed, one of the main tenets to what became known as Hy's law[2,3] is that a reasonable attempt be made to exclude alternative causes. Causality assessment of drug-induced liver injury (DILI), however, involves more than just eliminating other possible causes of hepatic injury. Many elements are involved in the process, several of which were codified in a consensus opinion statement of several international DILI experts, including Dr. Zimmerman, under the auspices of the Council for International Organizations of Medical Science (CIOMS), which was sponsored by the Roussel Uclaf Pharmaceutical Company almost 25 years ago[4–6] (Table 1).

While noting his participation in the conference, Zimmerman does not specifically mention The Roussel Uclaf Causality Assessment Method (RUCAM) by name in his seminal textbook on the subject.[1] Although many of the same diagnostic criteria that constitute RUCAM are enumerated in his chapter on diagnosing DILI, Zimmerman emphasizes that "some flexibility in applying (these criteria) is warranted." This statement, acknowledging the relative inflexibility of RUCAM scoring, has been cited as the main reason why Zimmerman declined to be listed as an author on either of the consensus statement manuscripts, a request also made by and granted to Willis Maddrey (personal communication, March 2014). Nevertheless, the same basic elements chosen for inclusion in RUCAM 25 years ago still constitute much of the basis for determining causality of DILI today. However, one can certainly ask this question: If these criteria were not considered definitive by Zimmerman, Maddrey, and others, what role should RUCAM (or other similar causality assessment methods) play in assigning causality at present, and how does it compare to the expert opinion process in adjudicating DILI?

RUCAM: Problems and Pitfalls

The causality assessment of DILI began more as an art form than a science,[7] although the use of early methodologies involving nonorgan-specific drug reactions, such as the Naranjo scale, are now considered inadequate for determining liver-specific damage.[8,9] Indeed, all of the current causality assessment methods are imperfect.[7,10–12] As acknowledged by Kaplowitz, much of our initial attempts to establish causality with respect to DILI involved a measure of "guilt by association" and in some situations, "suspicion [was] more important rather than proof."[13] This often is still the case; a truly definitive means of establishing a diagnosis such as the existence of an accurate DILI biomarker remains unavailable.[14–16] Apart from cases where drug-specific antibodies or adducts can be found as a means to "prove" causality (eg, halothane, ticrynafen),[13] our ability to assign the causality of an hepatic-related event to a specific drug has generally relied on the basic elements contained in RUCAM. However, whereas a positive rechallenge response was the

Abbreviations: ALF, acute liver failure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CBD, common bile duct; CIOMS, Council for International Organizations of Medical Science; CMV, cytomegalovirus; CYP, cytochrome; DILI, drug-induced liver injury; DILIN, Drug-Induced Liver Injury Network; EBV, Epstein-Barr virus; FDA, US Food and Drug Administration; HACs, hepatic adjudication committees; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HEV, hepatitis E virus; HLA, human leukocyte antigen; LAEs, liver-associated enzymes; NAFLD, nonalcoholic fatty liver disease; RUCAM, Raoussel Uclaf Causality Assessment Method.

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TABLE 1 RUCAM Diagnostic Elements and Point Values[5,6]

Appropriate temporal relationship (time to onset; latency)	(+1 to +2)
Clinical course after drug withdrawal (dechallenge)	(−2 to +3)
Presence of DILI risk factors (age > 55, alcohol, pregnancy)	(0 to +2)
Presence or absence of concomitant hepatotoxic drugs	(0 to −3)
Search for and exclusion of nondrug causes	(−3 to +2)
Prior reports/information confirming the suspect drug's hepatotoxicity	(0 to +2)
Response to readministration (rechallenge)	(−2 to +3)

Scoring: Highly probable > 8 points; probable 6-8 points; possible 3-5 points; unlikely 1-2 points; excluded ≤ 0 points.

basis on which RUCAM was validated,[6] many believe it is an over-weighted criteria, and we have largely moved away from intentionally reexposing patients for fear of precipitating an even more severe hepatic reaction. In addition, numerous other pitfalls and challenges inherent in the interpretation of the RUCAM have been noted by several groups[7,12] (Table 2).

Efforts aimed at simplifying RUCAM generally have been unsuccessful,[7,12,17] and although RUCAM has emerged as the most accurate method, it is not known how reproducible RUCAM is in the hands of nonhepatologists. Given the expertise needed to interpret many of its elements and ambiguities, it is unclear whether health care professionals unfamiliar with the nuances of DILI would be able to calculate a meaningful score. Whereas Sgro et al[18] found that general practitioners could be taught to detect and report DILI using a global imputability method, the rigor by which DILI was adjudicated was not detailed. Moreover, the fact that DILI experts frequently disagree when evaluating the same information[19,20] suggests that nonhepatologists would have even more difficulty.

Expert Opinion of DILI in Clinical Trials and Postmarketing Experience

There are a number of areas in the causality assessment process that require expert evaluation and interpretation (Table 3). Many involve situations or findings that either are not included in the RUCAM criteria or have subtleties that create diagnostic difficulties, even for those individuals with experience in DILI adjudication. Such issues are routinely discussed and debated by members of hepatic assessment committees (HACs) formed to adjudicate hepatic events that occur in the clinical trial or postapproval setting. In such expert discussions, differences of opinion often arise, but they usually are able to be resolved collegially in order to achieve a unanimous or consensus opinion that is a necessary part of the regulatory review of the drug. Only rarely has RUCAM been used in a clinical trial.[19] Prior knowledge of the "signature" of DILI for the drug under question either does not exist or may be based solely on preclinical toxicology, which often is difficult to correlate with the human

TABLE 2 Pitfalls and Ambiguities in RUCAM Scoring (after 7)

RUCAM Criteria	Comment
1 Age > or < 55 years are arbitrary cutoffs.	Many cases occur under age 55.
2 No specific amount of alcohol use defined.	Uncertain if alcohol is risk factor or a confounder.
3 Role of pregnancy in DILI undefined.	Unclear if pregnancy is risk factor or confounder.
4 Narrow latency period for maximal points.	Fewer points awarded if < 5 days or > 90 days.
5 Does not account for delayed reactions occurring >15 days after stopping a drug.	(eg, amoxicillin-clavulanate occurring up to 6 weeks after use)
6 Narrowly defined responses to dechallenge.	Decreases from peak ALT values are arbitrary.
7 The 8 nondrug exclusions are incomplete.	Does not include specific mention of hepatitis E, etc.
8 Hepatotoxicity in the product label may score higher than published reports.	RUCAM was not designed for drugs in clinical trials.
9 Rechallenge response not well-defined.	Doubling of ALT is arbitrary criterion.
10 Liver histology not considered.	Liver biopsy information is not taken into account.
11 Does not allow for diagnosis of tolerance or adaptive response while drug is continued.	No dechallenge criteria to evaluate.

Abbreviation: ALT, alanine aminotransferase.

TABLE 3 Controversies in Assigning Causality for DILI That Require Expert Interpretation

- Attributing tolerance/adaptation to the drug in question
- Diagnosing acute DILI in the setting of chronic liver disease
- Diagnosing DILI that might occur after a drug has been discontinued
- Determining when to initiate a workup for alternative causes, and how extensive the evaluation should be based on the injury pattern and height and ratio of the LAEs
- Interpreting histologic findings
- Determining the amount of alcohol that constitutes a risk factor
- Factoring in the influence of concomitant meds, drug--drug interactions and polypharmacy
- Differentiating DILI from an acute exacerbation of viral hepatitis, such as HAV, HBV, HCV, HEV, CMV, EBV
- Determining the influence of hepatobiliary malignancy, gallstones, CBD strictures, etc on LAEs
- Interpreting fluctuations in aminotransferase levels and ALT:AST ratios
- Taking the absolute height of ALT and AST into consideration and how to best interpret increases above elevated baseline values
- Interpreting atypical or negative rechallenge responses
- Interpreting atypical dechallenge responses that may not conform to RUCAM choices
- Interpreting the dechallenge response after suspected drug-induced autoimmune hepatitis
- Interpreting the exact role played by pregnancy in awarding points in RUCAM
- Assessing herbal and dietary supplement- suspected DILI

Abbreviation: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CBD, common bile duct; CMV, cytomegalovirus; EBV, Epstein Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus, HEV, hepatitis E virus; LAEs, liver-associated enzymes.

experience.[3] In the case of applying RUCAM criteria to ximelagatran, it was only with increasing familiarity with the methodology over the course of the clinical study that the adjudicators were able to improve their concordance with the case assessments, although the attempt served to highlight the overall shortcomings of RUCAM.[19] There are many examples in the literature where the expert panel

TABLE 4 Possible Modifications of RUCAM to Improve Its Accuracy (with selected references)

- Compatible hepatic histology[25,26]
- Interpreting the risk of underlying liver disease[27,28]
- Increased DILI risk associated with higher daily drug doses[29]
- Increased DILI risk of higher lipophilicity and drug dose ("Rule of two")[30]; or greater degrees of hepatic metabolism[31]
- Presence of DILI biomarkers from proteomic (32) or cytokine analytes[16,33]
- Presence (or absence) of hypersensitivity hallmarks (fever, rash, eosinophilia)
- HIV status
- Presence or absence of pharmacogenetic susceptibility factors (eg, HLA, CYP polymorphisms)[34]
- Presence of blood levels of the suspected drug
- Positive (or negative) lymphocyte transformation tests (where available)[a]
- Is the suspect drug listed in LiverTox?[35]
- Fractionation of total bilrubin (into direct and indirect) to exclude Gilbert's syndrome, hemolysis, etc
- Fractionation of serum alkaline phosphatase to confirm hepatic origin
- Use of standardized minimal elevations of LAEs to define severe DILI[36]
- Availability of long-term follow-up information to assess outcomes
- Development of a computerized point scoring system to avoid ambiguities

Abbreviations: CYP, cytochrome; HLA, human leukocyte antigen.
*Neither available in the United States nor approved by FDA.

process (rather than RUCAM) was used by the US Food and Drug Administration (FDA) and other groups to assess the hepatotoxicity of newly approved drugs such as troglitazone,[21] bromfenac,[22] and telithromycin.[23]

RUCAM has neither been updated nor modified to improve its diagnostic accuracy in more than 20 years, although it is known to underscore DILI cases and overscore non-DILI cases.[20] As a result, whether its predictive value would be improved by adding more diagnostic criteria remains untested. Table 4 lists a number of clinical criteria that are routinely taken into account in the performance of an expert opinion DILI adjudication, as well as a number of pharmacological elements whose inclusion could potentially enhance the existing RUCAM scoring system.

DILIN Expert Opinion Methodology

Recognizing that RUCAM does not offer a perfect solution to determining causality, the US Drug-Induced Liver Injury Network (DILIN) has incorporated a structured expert opinion process with the standard elements in RUCAM. Their hybrid adjudication method, as defined by Rockey et al,[20] includes prospectively reviewing the clinical data from the cases that are submitted to the registry—all of which were initially judged by an expert in DILI. For alternative causes that may not have been excluded at the time of the initial hepatic event, additional testing is obtained within the first 6 months of the injury to try to uncover other forms of hepatitis, both viral and metabolic. Three reviewers work independently to assess each of the cases; if there are disagreements or discrepancies, discussions among the reviewers are conducted to resolve any issues

TABLE 5 Definitions of the DILI Network's Diagnostic Probabilities[20]

Unlikely	< 25% likelihood drug was responsible. Evidence that etiologic factor other than drug caused injury
Possible	25%-49% likelihood drug was responsible. Evidence for drug is equivocal but present.
Probable	50%-74% likelihood drug was responsible. Preponderance of evidence linking drug to injury
Highly likely	75%-95% likelihood drug was responsible. Evidence for drug causing injury clear and convincing but not definite
Definite	> 95% likelihood drug was responsible. Evidence beyond reasonable doubt for drug being causal

and arrive at a final assessment. They use a percentage probability score to define cases as unlikely, possible, probable, highly likely, and definite (Table 5).

Interestingly, the DILIN group does not have a category for "excluded" or "unrelated" because all of the cases are initially submitted with the understanding that they were at least possibly related. This is borne out by the fact that in the current DILIN registry results very few cases have been considered unlikely by the reviewers,[20] making the DILIN method analogous to an "expert's expert opinion" process. Working together over time, the agreement between reviewers has been quite good. Although interobserver variability exists for both adjudication methods (kappa scores of 0.6 for DILIN and 0.34 for RUCAM),[20] the DILIN consensus process offers the ability to collect additional data (including the results of biomarkers, viral serology)— and outcome results over the course of the next 6 months (and longer) to ensure that all possible nondrug factors can be sought and eliminated. Knowledge of the long-term outcome of the suspect drug is key to understanding the course of DILI in many scenarios and is ensured by the expert consensus DILIN process.

A similarly structured causality assessment method was also employed by members of the Spanish DILI Registry. Cases considered to be drug-related by expert clinical judgment were then assessed by CIOMS/RUCAM scoring in this group's latest study to identify a novel composite algorithm to predict acute liver failure (ALF) using an improved definition of Hy's Law.[24] Only cases classified as likely due to DILI by CIOMS were used in the analysis (91% being either probable or highly probable; 9% judged to be possible). Although their dataset was not assessed using CIOMS/RUCAM scoring alone, the approach used to assess whether their proposed "new" Hy's Law would increase the sensitivity and specificity of predicting ALF could still be considered to be weighted heavily by expert opinion because that method was used to identify the initial DILI cases. As such, it lends further support to the notion that expert opinion remains the preferred method to select and adjudicate drug-related hepatotoxicity.

Summary and Future Directions

RUCAM was designed by an expert panel, but as the saying goes: A camel is a horse designed by a committee. In a sense,

TABLE 6 Comparison of RUCAM, Clinical Practice Expert Opinion, and DILIN Expert Consensus

Criteria	RUCAM	Clinical Practice	DILIN
Adjudication process	Semi-objective quantitative scoring method	Individual expert opinion	Expert consensus
Clinical setting	In real time? In a clinical trial? Retrospective analysis?	Immediate: at the bedside or in the clinic	Case submitted within 6 months of acute DILI onset
Clinical implications	Regulatory? For publication? Mechanistic studies?	Determine if the drug should be stopped vs continued with close monitoring	Epidemiologic data.Identification of pathophysiology and risk factors
Reviewers	1	1	3
Adjudication categories	Highly probable, Probable, Possible, Unlikely, Excluded	Likelihood of 50% or higher usually needed to support clinical decision	Definite, Highly likely, Probable, Possible, Unlikely
Duration of follow-up	1--3 months	Days to months	6 months (or longer)
Nondrug etiologies excluded	Many, but not all (6 group 1 causes: acute HAV, HBV, HCV, biliary obstruction, alcoholism (AST:ALT > 2), ischemic hepatitis; and two group 2 causes: complications of underlying disease, additional viruses as clinically suspected; does not incorporate histology	Usually all (depending on the extent of the evaluation); can include histology	All (including CMV, EBV, HCV, HEV, etc), utilizes hepatic histology read centrally (if available) and long-term follow-up with potential results from biosample testing
Allows for diagnosis of drug-tolerance or adaptation	No	Yes	Yes
Reliance on a positive response to rechallenge	Strong	Rarely	Rarely
Ease of use and generalizability	Not formally tested outside of expert hands	Dependent on clinical experience	Limited to DILIN experts
Reproducibility	$\kappa = 0.34$ May improve with increasing use and familiarity	Unknown for a single expert; improves with discussions to arrive at consensus when more than 1 expert involved, especially when dealing with the same drug (eg, a hepatic adjudication committee for a clinical trial)	$\kappa = 0.6$ Involves discussion to develop a consensus opinion when individual adjudications are divergent

CMV, cytomegalovirus; EBV, Epstein-Barr virus; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HEV, hepatitis E virus.

This table has been adapted based on "RUCAM Vs. Expert Opinion," presented by RJ Fontana at Hepatotoxicity DILI Conference XIV: Predicting Serious Drug-induced Liver Injury in Patients, Hyattsville, Maryland, US, March 19, 2014.

the question of whether RUCAM or expert opinion is the best process to diagnose DILI can be viewed as knocking a straw man down. Because RUCAM was developed by expert consensus, and most of its elements still form the basis of any initial expert opinion adjudication process, what we end up debating is whether or not either process is sufficient in and of itself to confirm DILI. The short answer is no—adjudication remains more of an art rather than a science. RUCAM does not allow for the flexibility that expert opinion permits, especially in interpreting the numerous gray areas that invade clinical settings, as indicated in Tables 3 and 4.[25–36] Individual expert opinion is certainly not infallible, as demonstrated by the fact that HACs and other liver safety-assessment panels are usually composed of at least three or more DILI experts. The DILIN approach of combining an expert consensus process with the basic RUCAM elements seems the most reasonable for the present time and is incorporated into the discussions undertaken by most expert adjudication panels. The value of expert opinion is the ability to recognize atypical clinical features and presentations, such as the delayed DILI seen with amoxicillin-clavulanate after it has been discontinued; the prolonged latent periods associated with the autoimmune-type of injury described with minocycline and nitrofurantoin; the often nonspecific histologic findings present in liver biopsies; and the difficulties in interpreting acute DILI in the face of underlying NAFLD, viral hepatitis, and other chronic liver diseases. Moreover, being able to recognize nondrug causes of acute liver injury is equally important, if not more. Determining which features constitute hepatic injury from alcohol, muscle damage, choledocholithiasis and passage of a common duct stone, NAFLD, exacerbations of viral hepatitis B or C, autoimmune hepatitis, and other common disorders can be quite challenging, especially in a scenario involving a potentially hepatotoxic agent or study medication. Acute hepatitis E has been shown to mimic DILI cases and should be looked for routinely[37] (Table 6).

Although it remains impossible to "prove a negative" when a diagnosis of DILI is concerned, the discovery of a validated diagnostic biomarker for DILI may make any causality method obsolete in the future. Until such time, however, the collection and storage of serum or other biosamples for later study to establish causality by genetic or proteomic means remains the best way forward,[38] and at present, expert opinion or expert consensus is favored over RUCAM.

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