Published in final edited form as:

Curr Hepatol Rep. 2018 September ; 17(3): 276–282. doi:10.1007/s11901-018-0416-8.

Novel Approaches to Causality Adjudication in Drug-Induced Liver Disease

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Abstract

Purpose of Review—Drug induced liver injury (DILI) is a complex diagnosis dominantly based of exclusion.

Recent Findings—Currently available causality assessment instruments are considered to be suboptimal. Expert opinion appears to be best method to adjudicate causality, but is impractical to implement on a wide scale basis. Thus, new approaches are needed, for example improving the specificity of current scoring systems. A further option would be to develop a system that utilizes computer-based scoring - which would reduce human error. Additionally, it would be ideal to have available drug specific scoring systems, based on drugs' characteristic “phenotypes” (presentation and pattern of injury). Eventually, a validated system could be integrated within the electronic health information system.

Summary—This review highlights an avenue to an improved Causality Assessment Tool

Keywords

Causality; Drug induced liver injury; scoring system; liver disease

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Compliance with Ethical Standards

Conflict of Interest

Hans L. Tillmann reports that his spouse is a full-time employee of AbbVie, reports grants from NIH-NIDDK, during the conduct of the study, reports personal fees from AbbVie, Abbott, and Gilead from stocks, and reports personal fees from Novartis and Novo Nordisk for consulting, outside the submitted work; Huiman X. Barnhart, Jose Serrano, and Don C. Rockey declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors

Introduction

Drug induced liver injury (DILI) remains an important challenge in clinical practice, in drug development, and in post marketing surveillance. Hepatotoxicity is a leading reason for market withdrawal of licensed drugs, both worldwide and specifically by the FDA [1,2]. Although the FDA has not licensed any new drug that needed to be withdrawn due to hepatotoxicity in the past decade, DILI is an ongoing concern in this field. For example, in February 2018, the European Medicines Agency (EMA) recommended the removal of flupirtine from the market due to ongoing concerns about severe DILI^[3]. Furthermore, even for approved drugs, DILI accounts for substantial morbidity and mortality in the US and worldwide ^[4,5, 6, 7].

It is well appreciated that liver test abnormalities may result from many different types or causes of liver disease ^[8,9,10]. Unlike diseases such as viral hepatitis, where a single diagnostic test may confirm or exclude the diagnosis with high sensitivity and specificity, DILI is a diagnosis based on suspicion of an adverse drug reaction and exclusion of competing causes of liver injury. Because of the difficulty in diagnosing DILI, several causality assessment tools (CATs) have been developed. They all are based on point-scoring systems, (e.g., the “Roussel Uclaf Causality Assessment Method (RUCAM)”, the “clinical diagnostic scale” (CDS), and the “Digestive Disease Week Japan 2004 scale (DDW-J scale)) ^[11, 12, 13]. While these scoring systems have considerable value, they are limited in inter-rater reliability and even intra-rater reproducibility. ^[14] Currently, a structured expert-opinion based approach, such as described and utilized by the NIH-sponsored Drug Induced Liver Injury Network (DILIN), appears to be superior to RUCAM ^[15]. Unfortunately, a major drawback of the expert opinion approach is that it is not widely available in clinical practice and thus not generalizable. Thus, improved causality assessment tools are needed.

Here, we present a review that highlights a conceptual framework focused on development of novel causality assessment approaches. We believe that an ideal DILI causality assessment tool should be **drug-specific** (when possible), **programmable** (to minimize human error), **adjustable** (amendable to incorporate new information).

Approaches to improve causality

Computerization of Causality Tools

An issue with of the currently used causality assessment tools is their reproducibility ^[16], as the calculations and interpretation of several elements used in the assessment tool are subject to subjectivity. For example, RUCAM, one of the most commonly used causality assessment tools, is subject to substantial variability not only across different clinicians, but also when used by the same individual at different times ^[14,15].

An ideal approach to overcome variance in interpretation of clinical data used for instruments such as RUCAM would be to computerize the scores for specific components (latency, injury peak time, secondary liver markers increased, de-challenge). For example, exact dates would be entered for dates of drug use, onset of symptoms, onset of laboratory abnormalities, etc, and a computer could automatically calculate timing. This is not a trivial

task due to the complexity of the variables to be considered as well as subtle nuances in timing features of latency and dechallenge

An advantage of computerization of any causality tool is reduction of human error in calculation of scores. We have developed a preliminary computerized RUCAM tool that provides scores for all drugs taken by the subject (data not shown). While this preliminary version still requires further testing and remains imperfect, its development demonstrates that RUCAM scores can be assigned by a computer based process. Further, one advantage of such a system is that scores can be calculated simultaneously for several implicated and/or possible concomitant drugs. This is an important feature, because it may bring to attention drugs that might otherwise be overlooked.

Optimization of existing approaches

Another option to improve causality assessment would be to enhance currently used causality instruments. For example, for RUCAM, inclusion of the presence or absence of extrahepatic manifestations consistent with an immunoallergic reaction such as rash, fever, eosinophilia, cytopenia and arthralgia may improve its accuracy.

Another fairly simple way to improve current causality assessment tools would be to refine the variables currently used to calculate scores. For example, with exception of a very few drugs, DILI is uncommon in situations where latency is long (i.e., > 6 months). RUCAM assigns the same point score for latency for a drug taken for greater 10 years or 91 days; for most drugs, the latter scenario would be more consistent with DILI. Likewise, onset within 14 days of taking the drug may deserve a higher score than onset within day 90. A computerized process in this situation could prove to be even more precise because a continuous scale (as opposed to an interval scale) could be used, allowing for greater specificity. Another example is with dechallenge - a 50% improvement within a very short time, e.g., 1 or 2 days, is not highly characteristic of DILI, and likely does not deserve the same point score as a more typical dechallenge interval.

The same can be considered for very short latency, which is not typical of DILI. Currently, with RUCAM, liver injury occurring within hours or a day from exposure gets the same score as injury occurring within 4 days. Thus, such ultra-short latencies (0 to 2 days) may not deserve point allocation as with the current RUCAM system. It is more plausible that, as in the CDS approach [12], a very short latency (<4 days) is less likely to be DILI.

An additional opportunity to improve current causality instruments is to better quantify the intrinsic likelihood that a drug is hepatotoxic. Several approaches are possible; one approach is to attribute hepatotoxicity based on the number of reported cases [17]. A previous study assigned a relative hepatotoxicity risk category based on review of the literature as follows: a) drugs with 50 reported cases, b) drugs with 12–49 reported cases, c) drugs with 4–11 reported cases, d) drugs with 1–3 reported cases; and e) no reported cases or insufficient time since approval for exclusion of drug's potential for DILI [17].

Alternatively, intrinsic hepatotoxicity might be assigned to a drug according to daily dose and a drug's lipophilicity. A "rule of two" has been proposed where one criterion is a daily

dose >100mg and second criterion is a high lipophilicity (>3logP octanol-water partition coefficient); if both are fulfilled, a drug is likely to cause DILI [18]. This allows for hepatotoxicity assessment also for newer drugs, where there are an insufficient number of patients having received the drug to assess hepatotoxicity. The current “rule of two” uses simple categories (1 or 2). Further, improvements, could be made to develop a continuous scale and/or other parameters could be added - such as metabolic modifiers (known hepatic metabolism of the drug, risk of liver accumulation, bioavailability, presence of reactive metabolites, inhibition of specific excretion pathways, etc...)

Improved handling of competing causes of liver injury may also be possible. For example, it is very likely that some competing causes of liver injury may be more important than others, and moreover that this may vary depending on the type of biochemical liver injury. For example, DILI in a cholestatic pattern is unlikely to be confused with acute viral hepatitis A, B, or C, and it may not be critical to exclude these diseases in certain situations. Additionally, diseases that cause a cholestatic biochemical phenotype do not need to be excluded when the DILI pattern is purely of hepatocellular injury.

Approach to drug specific DILI-Causality assessment tools

A current limitation of available tools is that all current scoring systems use a one size fits all approach for all drugs. For example, current scoring systems discriminate between hepatocellular injury patterns and mixed/cholestatic injury patterns with regard to time-intervals (i.e. latency and dechallenge intervals); however, data supporting this approach are not available. One study suggested that there may not be significant differences in latency based on biochemical pattern, while there are major differences between drugs [19]. Furthermore, it is well appreciated that different drugs have different clinical phenotypes, with regard to latency, biochemical pattern, immunoallergic features and other characteristics.

As more knowledge emerges about DILI, it can and should be used to improve DILI causality assessment. One approach may be to use data generated from large registries such as DILIN [5], the Spanish DILI registry [20], or the Latin American registry [21]. Such databases could be used to provide information with which to create algorithms that could be used to improve DILI assessment.

To overcome the limitation caused by a “one size fits all” approach, it may be possible to develop drug specific algorithms. Drug specific algorithms would also be especially helpful in light of increasing polypharmacy [22,23], where it will not only be important to identify that a DILI event occurred, but to elucidate which drug is the likeliest culprit.

A drug specific phenotype may be defined by latency, dechallenge, other time intervals defining the progression of the injury (i.e. onset to peak, time enzymes remain elevated,) R-value (ratio between ALT and AP), but may also include biochemical features such as AST/ALT ratio [24], or other liver test patterns, as well as the presence or absence of extrahepatic manifestations. Such a drug specific phenotype could then be used in causality assessment tools, which would in theory have different algorithms for different drugs, based on unique DILI phenotypes. We would propose to develop such tools using the most likely

DILI cases graded as highly likely or definite. Alternatively, one could include other cases, but give less likely cases a lower weight. The latter would make a complicated approach, however, even more complex.

To improve the utility of published cases and case series, it would be desirable for new publications to provide detailed information about as many clinical parameters as possible - such as latency from drug start to onset, from drug stop to onset, dechallenge as time to 50% decrease from peak for ALT and AlkPhos, and time to normalization, R-value and the “de Ritis” ratio (AST/ALT ratio), and presence or absence of various extrahepatic manifestations.

Data driven development of a causality assessment tool

Because key clinical variables that might be used to assess in DILI adjudication are continuous, it is possible that data from *bona fide* DILI cases could be used to develop rigorous metrics consistent with DILI; these metrics can then be used to adjudicate any case of interest. For example, a certain drug (or a group of drugs) would be expected to have a latency that falls within a typical range; in the instance of amoxicillin/clavulanic acid, the published latency was 2 to 12 weeks in 97% of cases [25], which could be further condensed to a smaller core. Such a “fingerprint” can be derived from available data, and is likely to be robust. Thus, the likelihood that the true latency for the drug falls within a specific range could be assigned a specific value - and this could then be used to assess the relative likelihood of DILI in a patient who had received that agent. Thus, the distribution of the continuous variable from clear cut cases (i.e., definite and highly likely DILI) helps define the causal relationship between the drug and the injury. An algorithm can be developed to reflect relative congruency of the variable (in this instance, latency) with that of the case with a suspected DILI. A score, based on the fit of the case in question with that of known respective drug phenotype, can be assigned. The closer the fit, the higher the assigned score, and the poorer the fit, the lower the score. Such an approach is likely useful for many drugs, but may not work for all drugs. For example, nitrofurantoin has very atypical and highly variable latency features, and developing a robust latency fingerprint, this may not apply or be more complex due to bimodal distribution in latency [26].

Additionally, the presence of other features - such as immunoallergic reactions -- could be included in the algorithm. This may include presence of rash, fever, abdominal pain, eosinophilia, or the presence of autoantibodies (ANA, SMA, AMA, LKM, SLA). Because such variables are categorical, an algorithm could be based on the likelihood of features being present. For example, if 70% of previously adjudicated cases had rash due to a drug A, but only 20% of adjudicated cases had rash due to drug B, then the algorithm would assign a higher score to a case with rash due to drug A than the score to a case with rash due to drug B.

Overall these features can be used to develop data-driven algorithms, which then can explore individual drugs for being likely or unlikely culprits (Figure 1).

Variables Potentially Important in DILI-causality assessment

A number of clinical (and other types of) variables could further improve drug specific causality assessment (Table 1). Several of these are highlighted in some detail below.

Genetics—While a universal genetic marker to differentiate DILI from other causes of liver injury has not emerged, there is clear evidence that genetic factors play a role in DILI. For example, the odds ratio is estimated to be 2 for the association of HLA A*02:01 with DILI due to amoxicillin/clavulanate, while the odds ratio may be up to 80 for the association of HLA B*57:01 with DILI due to flucloxacillin [27]. Interestingly, HLA type, e.g., HLA-B*57:01, predisposes to severe abacavir associated hypersensitivity, but not DILI, while the same HLA-type predisposes patients to DILI when exposed to flucloxacillin [28]. Currently, no genetic association with DILI has yet been translated into the development of a preventive intervention in clinical practice. However, the strength of the genetic association could be used in causality assessment, where the presence of a specific susceptibility genetic maker would increase likelihood, while its absence would be associated with lower DILI likelihood.

Gender—Limited data on gender and DILI are available, but DILI due to some specific drugs may occur predominate in certain genders. For example, androgenic steroids, which cause a typical biochemical DILI pattern (so called “bland cholestasis”, have been implicated as a cause of DILI only in men, although women, too, have taken androgenic steroids. On the other hand, significant DILI due to β -interferon appears to occur only in women. Of note, while mild elevations of liver enzymes were frequently observed in men who took on β -Interferon, [29] severe DILI was only been reported in women [30,31].

Race—Race could also play a role in causality. For example, 112/123 DILI cases attributed to amoxicillin/clavulanate were Caucasians (CI 84.7 to 94.9%) compared to 29/45 cases attributed to isoniazid were Caucasian (CI 49.7–76.7%) with no overlap in the respective confidence intervals, suggesting a significant association with race.

Potential Risk Factors for DILI—Risk factors for DILI such as the presence of alcohol consumption or age, are likely to be complicated. These may be either drug-specific or perhaps universal for some drugs. An example of a possible drug-specific risk factor is older age in the case of amoxicillin/clavulanate or isoniazid associated DILI [32, 33], while younger age may be a risk factor for valproate and daptomycin associated DILI [34]. Another commonly considered risk factor is the ingestion of alcohol, although in a recent study alcohol consumption was found neither to be a specific risk factor nor a clear factor for adverse outcome in a recent report from the US DILI-Network [35]. Overall, examination of further risk factors requires further evaluation.

Laboratory Testing—Drug lymphocyte stimulation testing has been used with success in Japan but is difficult to reproduce. A recent published approach appears to be promising [36,37]. This test is based on monocyte-derived hepatocyte-like (MH) cells derived from fresh blood. The MH cells, when exposed to suspected and not suspected drugs, react dominantly with the clearly suspected drugs. A recent study using this assay reported a 92%

sensitivity and 100% specificity for identifying a drug that caused liver injury, which was confirmed as DILI causing agent in cases of inadvertent re-exposure [38]. Such a test would be difficult to generalize to routine clinical practice but could be used in certain situations in causality assessment, particularly when it is crucial to ascertain the causality of a specific drug.

Conclusion

DILI diagnosis remains a challenging diagnosis of exclusion. With growing sets of data available to study DILI, there are great opportunities to evaluate variables that may be important in causality assessment. Further, it is likely that as these data sets grow more robust, they can be leveraged to develop programmable DILI-causality assessment tools (DILI-CAT), which can take drug-specific DILI phenotypes into account. An improved DILI-CAT will be most helpful for the non-expert but will likely also help experts to make better informed decisions.

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Figure 1.
Flow of Data-Driven DILI Causality Assessment

Table 1

Potential factors to consider to include into future drug specific causality tools:

AST/ALT ratio at onset
AST/ALT ratio at ALT peak
gGT values
Age as risk factor
Alcohol consumption as risk factor
Genetics
Race
Gender
Viral infections as risk factor or epiphenomena (HCV, HBV, & herpes viruses especially EBV and HHV-6)
Additional time segments
Presence of autoantibodies (ANA, AMA, SMA and/or LKM)
Inclusion of certainty criteria based on: <ul style="list-style-type: none"> a) number of cases a) narrowness of phenotype/intervals