Drug-induced liver injury, mortality, and liver transplantation: is it reasonable to use a global introspection causality assessment?

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Drug-induced liver injury (DILI) is a challenging topic in hepatology, with high expectations on studies bringing additional data in support of disease characterization. At least since 2005 it has been documented that a majority but not all patients with DILI recover from their disease following drug cessation. Indeed, a fatality rate around 10% is expected among patients who were studied for the first 6 months. In 2017, this knowledge stimulated Hayashi *et al.* (1) to analyze the fatality rate of DILI patients within two years after DILI onset. With a fatality rate of 9.8%, the online study under discussion showed similar results (1) and confirmed data on the first six months from two large European registries in 2005 (2,3). These two pioneering reports were based on DILI cases from Spain (2) and Sweden (3). Both groups used Roussel Uclaf Causality Assessment Method (RUCAM) (4,5) to validly and objectively assess causality (2,3). With conclusions based on results using global introspection, the study under discussion provides data raising questions (1). These focus on causality assessment methods of DILI cases and point out other aspects of interest that merit consideration.

Global introspection method

Rather than using the original RUCAM (4,5) or better now the updated RUCAM (6), Hayashi *et al.* assessed causality of the DILI cases through global introspection of DILI Network (DILIN) (1), with details and discussion provided elsewhere (7) and summarized recently (8). The DILIN global introspection approach is a multi-step expert opinion process to reach consensus among three hepatologists assigned to each case. This is hard to standardize and cannot be translated into daily clinical practice (7). Briefly, definite causality is defined as a >95% probability (described as beyond reasonable doubt), highly probable with a range of 75% to 95% (clear and convincing, but less than definitive), and probable with a range of 50% to 75% (preponderance of evidence support) (7). By definition not validated using a gold standard (7), this global introspection is subjective, does not use scored items, provides arbitrary causality percentage, and lacks transparency as to how final causality assessment levels were reached (1,6-9). This approach excludes any re-assessment and critical discussion (6). Its use is confined to the US and restricted to DILIN (6-9). Weaknesses include lengthy and lively conversations during the consensus process due to overlooked data, variations in reasoning, or data from new publications, making this method cumbersome, time-consuming, and costly (7).

Another study (10) illustrated shortcomings of the DILIN global introspection method but advantages of RUCAM, assessing causality in cases of suspected liver injury by a dietary supplement (DS) (9,10). Using RUCAM in the seven-case series, causality was unlikely in one patient, possible in four patients, and probable in two patients (10). This was in line with low or lacking RUCAM causality levels in similar DS cases (11-13). The DILIN global introspection method upgraded causality levels to definite, highly likely, and probable in 6/7 cases,

despite confounding variables in all cases: drug and DS comedications, incomplete exclusion of numerous alternative causes including chronic hepatitis B virus infection causing acute liver failure with the need of liver transplantation and lack of antiviral therapy of hepatitis B flares; intermittent DS use, and exclusion of hepatitis E virus (HEV) infection using HEV-DNA analyses (9,10). Overall, causality attribution remained questionable (9,10) since the type of DS used was not identified and chemical analysis was not done (10).

Prospective versus retrospective causality assessment

There is still uncertainty about the modalities of initial assessment, since presented data suggest a retrospective rather than a prospective causality assessment (1). This is evidenced by retrospective elimination of cases, including acetaminophen overdose and chronic liver diseases such as autoimmune hepatitis and primary biliary cholangitis (1). Problematic is also the information that out of 1,509 enrolled patients, only 1,332 underwent formal causality assessment, raising the question why the remaining 177 cases did not benefit from such initial assessment. Therefore, the criteria of overall case selection remain unclear.

Fatalities and liver transplantation

Among 1,089 cases assessed by global introspection, fatalities and/or liver transplant were described in 107 cases and constituted the fatality cohort (9.8%) (1). Within this cohort it remained unclear how many transplanted patients survived or died (1). Consequently, conclusions derived from results of this heterogeneous cohort lacking allocation to separate subgroups are likely not comparable to other studies on DILI outcome.

Causality grading

Among the heterogeneous fatality cohort of 107 cases, causality was definite in 15%, highly probable in 42%, and probable in 43% of the patients (1), using the global introspection method that provides only a vague causality grading of percentage ranges, as it is not based on individual quantitative item scorings (1). The causality levels (1) were therefore not based on clear items as shown in the descriptions outlined above. It is interesting to note that the

scientists using these obscure percentage ranges are those who criticize RUCAM that is based on defined items and a scoring system (14).

DILI as a primary or contributory role in fatal or transplant cases

Out of the 107 cases with a causality grading of probable or higher, DILI had a primary role in causing death or liver transplant in 68 cases, a contributory role in 15 cases, no role in 22 cases, and an unknown role in 2 cases (1). Among the 68 cases with DILI as a primary role, subgroups were established for acute liver failure (n=50), acute on chronic liver failure (n=5), chronic liver failure (n=9), and rapid cholestatic liver failure (n=4) (1). Problematic was the low case number of some subgroups, ranging from 5 to 9 cases, which do not allow a valid interpretation of the presented results; similarly, most P values did not show statistical differences, and it also remained unclear for which subgroups p-values were calculated (1).

Analyzing the 37 cases, for which DILI had a contributory or no role for fatality or liver transplant, numerous causes of death or liver transplantation were described (1). For the majority of the cases, malignancies were considered as causes of death but the time of first diagnosis was not indicated (1). Quantification of the contributory role of DILI for the other causes was not evaluated.

Ten-year assessment

For more than 10 years, cases were collected, starting in 2004 (1). At that time and over many years thereafter, facilities to validly exclude alternative causes such as pre-existing chronic liver disease or acute HCV and HEV infections may have been limited that would confound the DILI diagnosis. Problematic are cases with chronic liver diseases combined with DILI, which require specific diagnostic approaches (15,16), obviously not done in the study under discussion (1).

Case data quality

Data incompleteness is a common phenomenon in DILI cases, considered as a major issue when causality has to be assessed (17). Such conditions are factors confounding the DILI diagnosis, but the report under discussion does not address these confounders (1).

Table 1 Advantages and limitations of RUCAM

Advantages of RUCAM

    Prospective use

    Clinical approach

    User-friendly and cost-saving method

    Effective use without the need of an expert panel

    Timely use at the bedside of the patient

    Clearly defined key items of clinical features and course

    Full consideration of comedications and alternative causes

    Consideration of prior known hepatotoxicity

    Quantification of unintentional re-exposure results

    Hepatotoxicity specific method

    Structured and quantitative liver related method

    Individual scoring system of all key items

    Validated method (gold standard)

    Worldwide use: international registries, regulatory agencies and pharma companies

    Use in published DILI case reports and case series

    Transparent documentation

    Possible reevaluation by peers

Limitations of RUCAM

    RUCAM was not designed for suspected chronic DILI, which is mostly an unrecognized preexisting liver disease

Compilation from a previous report (6). DILI, drug-induced liver injury; RUCAM, Roussel Uclaf Causality Assessment Method.

Drugs causing suspected DILI fatality

Various drugs are listed for their primary role in DILI cases of acute liver failure in the supplemental *Table 2*, with isonicotinic acid hydrazide (INH) considered responsible for 9 DILI cases (1). This high number of INH cases is disturbing and requires better information of US physicians treating tuberculosis patients with antituberculosis drugs including INH. By careful monitoring, there should be good chances to substantially reduce fatalities by INH-DILI. Highly appreciated is the flow chart of the case series provided for the sake of clarity (1).

Suspected fatality of herbal and DSs

Cumulatively and with a primary role, 14 herbal and dietary supplements (HDS) were listed as causes of fatal liver injury or liver transplantation, but the suspected products were not listed (1). A previous DILIN publication reported liver injury by DS, whereby many patients used concomitantly several supplements, namely up to six (18). However, the DILIN global introspection method was not prepared to attribute causality to each concomitantly used DS (18), and this problem likely occurred in this study (1). Comedication with conventional drugs or HDS is a common feature in DILI cases (9-13), not specifically evaluated in the study under discussion (1).

Comparison with previous DILIN reports

It is outside the scope of this editorial to compare the data of the present DILIN paper (1) with the results of many previous DILIN reports dealing with prognosis of DILI. Among these is a DILIN report of 2014 on morbidity and mortality of DILI (19) and another DILIN publication of 2015 on DILI outcome (20).

RUCAM

Despite the fact that RUCAM is the worldwide most commonly used method to assess causality in cases of suspected DILI and herb-induced liver injury (HILI), as outlined in a recent report of the update of RUCAM (6), this method was not used by Hayashi *et al.* (1). By the systematic approach of defined items, RUCAM is widely used by stakeholders like treating physicians, DILI registries, regulatory agencies, manufacturers, and editors of scientific journals. Similarly, the new Prospective European Drug-Induced Liver Injury (PRO-EURO DILI) Registry launched in 2014 by Andrade also uses RUCAM, providing strong support for RUCAM (21). Advantages and limitations of the updated RUCAM were discussed (6) with details presented in a list (*Table 1*).

In addition, the recent prospective Indian study of Rathi *et al.* (22) on DILI with causality using RUCAM was qualified as a report of excellence (23). This study could serve as an example how the future cases of DILI should be analyzed and reported. Because the Indian study was a prospective cohort study, the suspected DILI cases were defined and data collection was complete. This resulted in high final RUCAM scores among the 90 patients (22). Causality was probable in 63/90 cases (70%), highly probable in 15/90 cases (18%), possible in 4/90 cases (5%), and unlikely or excluded in 8/90 cases (9%). The

prospective use of RUCAM facilitated early recognition of alternative causes in 8 cases: acute HEV in 3 patients, autoimmune hepatitis in 2 patients, with hepatitis A and B, and sarcoidosis in 1 patient each. HEV exclusion was systematically included in the investigations (22), not only because HEV is endemic in India but also because such exclusion is mandatory in any suspected DILI or HILI case (23).

RUCAM provides real time results during the patient is under medical care, with best data obtained if it is applied prospectively (6). To ensure quick causality assessment and to reduce interobserver and intra-observer variability, key elements and individual scores are defined. They were based on data analyses of DILI cases with positive rechallenge as gold standard also used to validate the method (4,5). Within the frame of the updated RUCAM and as a reminder, many other unscored alternative causes are listed which may confound the DILI diagnosis and should be excluded in any suspected DILI case (6). Overall, RUCAM-based causality grading is easily re-assessable by peers, does not require expert rounds, and has only few limitations that should be balanced with many advantages over other causality assessment methods (*Table 1*) (6). Furthermore, a recent review on DILI and HILI in 2016 (24) included a balanced perspective of causality assessment in DILI and the preferred use of RUCAM in its updated version (6). This is in support of previous statements that careful clinical evaluation of liver injury cases is mandatory (25). Of note, US scientists authored both reports (24,25).

Hayashi (14) has some reservations about the RUCAM published in 1993 (4,5) on details that were addressed in the updated version in 2016 (6). However, these concerns (14) are unjustified (6). In particular, R value to classify the type of liver injury clearly should be calculated the day when DILI is suspected and certainly not thereafter (6), time intervals consider start and stop of drug use (6), amount of prior daily alcohol use is clearly quantified for female and male patients (6) and details of known hepatotoxins are clearly defined, including how to access respective information on potentially hepatotoxic drugs (6).

As for any algorithms, some experts may favor adding or deleting key elements or changing scores for items, but considering such vague proposals for RUCAM would require a completely new method validation, using again cases with positive rechallenge, certainly a cumbersome approach. Discussions on changing key items or items scores do not target opinion-based global introspection approaches, which lack both features (7,14).

Conclusions

The study under discussion on death and liver transplantation in DILI is mostly confirmatory in line with many other reports on the subject. Lacking an individual item scoring system, the use of a subjective global introspection approach represents a diagnostic dilemma leading to questionable results and conclusions. Instead, for valid causality assessment of suspected DILI cases, RUCAM as the worldwide most commonly used tool for such cases should have been used to provide objective and transparent results.

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