

# Predicting fatalities in serious idiosyncratic drug-induced liver injury—a matter of choosing the best Hy's law

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The field of hepatotoxicity presents various interesting investigational challenging areas, such as pharmacogenetics and qualification through biomarkers. The ultimate goal is to achieve a true impact in the diagnosis of drug-induced liver injury (DILI) in clinical practice.

The complex interaction of drugs and host is one of the most exciting aspect that starts to be unveiled in hepatotoxicity. Indeed, the fact that the same drug induces different diseases in different individuals exemplify this complexity in DILI prediction.

Chen *et al.* have discussed in an elegant review both the risk of stratification of patient care and the relevant areas of future research aimed at filling these knowledge gaps (1).

Although we still have limitations in DILI diagnosis, researchers are actively working on several computer-based algorithms, mainly focused on cumulative scores of drugs metabolism risk factors, such as mitochondrial toxicity, inhibition of bile salt export pump (BSEP), among others. The development of a novel DILI cluster score is in progress, related to DILI prediction from multiple complimentary cluster and classification models, based on empirical and theoretical calculations of physicochemical properties of drugs, and their bio disposition (absorption/distribution/metabolism/elimination), as well as diverse substructural descriptors and known structural liabilities. The supply of improved scientific and regulatory guidance for the assessment of liver safety will depend on the validation of new diagnostic markers in DILI registries,

biobanks, and public-private partnerships (2).

An under-reported and still poorly explored field is that related to the outcome of long-term assessment of DILI associated with fatality, i.e., death or liver transplantation. This point should be seriously taken into account, since it represents a crucial issue regarding DILI disease burden.

The interesting and elegantly designed prospective study by Hayashi *et al.* (3) deserves some comments and raises several points for discussion. They explored DILI clinical course associated with fatality beyond 26 weeks after DILI onset and up to 2 years from the onset of liver damage, in 107 out of 1,089 (9.8%) patients belonging to the prospective US hepatotoxicity DILIN network (DILIN). Every single case was randomly assigned for an independent analysis review by two members of a Dead Review Subcommittee formed by eight members. Discrepancies among reviewers were solved through conference call discussion, of the whole Dead Review Subcommittee.

One of the main goals of this study was to establish whether fatality induced by DILI fell into the category of “primary”, “contributory”, or “not-associated” cause of death. A very interesting finding is that 68 out of 1,089 patients were linked to a primary cause of death induced by DILI, while a contributory cause was documented in 15 other. In the remainder 22 patients, DILI had no adjudicated role on fatality so that primary plus contributory to fatality added up to 7.6% of the series (83/1,089). Although antituberculous agents were frequently the culprit drugs

of acute liver failure (ALF), importantly herbal and dietary supplements (HDS) were the most prominent cause of DILI in this analysis. Older age, hepatocellular injury, and preexisting liver disease were more frequent in the fatality compared with survivors

Björnsson *et al.* also reported results on survival after acute DILI and concomitant jaundice in 685 patients enrolled in the Swedish Adverse Drug Reaction Advisory Committee between 1970–2004, with a mean follow-up of 10 years (4). They found that 23 out of 685 (3.4%) had been hospitalized, and 5 of them died due to liver disease. In this study, jaundiced patients who overcome a severe liver disease after an acute DILI episode was a rare finding. However, decompensated “cryptogenic” cirrhosis was detected in some patients associated with a fatal outcome, in which DILI might have played a very important role. Interestingly, duration of drug therapy before DILI diagnosis was found to be significantly longer in those patients who experienced liver-related morbidity/mortality during the follow-up. The frequent development of autoimmune hepatitis, as well as a protracted cholestatic/mixed pattern of DILI linked to normalization of liver tests during follow-up were two other interesting findings of this study.

Hayashi *et al.* (3) subdivided their cohort of patients with DILI playing a primary role in fatality into those presenting with ALF, acute on chronic liver failure (ACLF), chronic liver failure (CLF), or rapid, cholestatic liver failure (RCLF). In other words, investigating the means through which DILI played the primary role in fatality outcome was classified into different modalities. By carrying out this analysis, they clearly showed that not only patients died from ALF induced by DILI, but also DILI occurred after drugs had triggered an insult on previous CLF, or by developing both chronic liver disease or progressive CLF in a quarter of patients. In addition, a high percentage of patients died due to causes not related to liver disease. Malignancies accounted for over half of cases in 22 patients where DILI played no role in the outcome.

DILI linked to death or liver transplant triggered by non-ALF damage has not been well described in the literature. In the Hayashi study (3), 5 patients out of the 68 (7%) had underlying cirrhosis, thus subcategorized as ACLF. ACLF is therefore a recently described syndrome which represents a very important issue in clinical practice, by proving that drugs might trigger liver decompensation on preexisting cirrhosis (5). This syndrome has been associated with short-term survival in a high percentage of patients, and characterized by acute cirrhotic decompensation associated

with organ(s) failure. Although patients with ACLF are frequently alcoholics and usually have associated bacterial infections, DILI should be kept in mind as a less frequent but possible cause of liver decompensation (6).

Drug-induced chronic liver disease is one of the most interesting and poorly documented topics in the literature, and has also been addressed by the Hayashi study (3). They documented a fatality outcome in 9 out of 68 patients (13%), who died or needed liver transplantation after having developed CLF. Three out of 9 patients developed chronic liver injury associated with HDS products, and antibiotics were the culprit drugs in three of them. Interestingly, amiodarone and methotrexate have been documented causes of slowly developing progressive liver fibrosis in this study. Although no special features could be found in these 9 cases, they had lower initial transaminases and R ratios compared to those with ALF and ACLF.

Insidious DILI has also been studied by Andrade *et al.* (7), who analyzed the long-term outcome of sustained liver biochemical hepatocellular pattern abnormalities 3 months after drug withdrawal, or more than 6 months after cholestatic/mixed damage pattern induced by DILI. They followed 28 out of 498 patients submitted to the Spanish Registry with a chronic liver disease evolution between November 1995 and October 2005, which accounted for 5.7% of the total idiosyncratic DILI cases. The authors concluded that cholestatic/mixed liver injury was more prone to become chronic, while hepatocellular pattern presented features of more severe liver damage. Although cardiovascular and central nervous system groups of drugs were the most frequent ones implicated in DILI, amoxicillin-clavulanate, bentazepam, atorvastatin, and captopril were the most frequent causative agents. Both, more prospective-cohort and follow-up studies are needed to understand more the behavior of insidious DILI

The issue of chronicity after acute DILI was further examined by Medina-Caliz *et al.* in a prospective, long-term follow-up study (8). By including 298 out of 850 patients in the Spanish DILI registry who were followed up to DILI resolution with a maximum of 3 years they also analyzed the outcome of liver enzymes normalization, which aimed at finding a definition of DILI chronicity as well as the risk factors of DILI evolving to chronic outcome. The author's definition of chronicity, included abnormal liver laboratory tests, imaging studies, or histologic patterns, one year after DILI recognition. Although 273 of 298 (92%) patients resolved in less than 1 year from DILI onset, the remainder 25 (8%) developed chronicity. Older age, dyslipidemia,

and severe DILI were identified as independent risk factors for liver chronicity. Moreover, another interesting point observed by the authors was that alkaline phosphatase and total serum bilirubin values in the second month might help to differentiate chronic outcome from very prolonged recovery. All these findings reinforce the concept that 1 year is the best cut-off point to define chronic DILI-induced fatalities.

Nevertheless, the role of underlying diseases such as NAFLD interfering with the resolution of altered liver biochemical parameters is usually a confounding factor to be considered during the follow up of patients suspected of DILI.

One of the most attractive goal of Hayashi's work (3) was to compare the original Hy's law coined by Hyman Zimmerman, with the modified, nR form proposed by the Spanish DILI Registry investigators (9).

Reliable predictive variables of severe outcome remain a challenging issue in clinical practice. ALF associated with idiosyncratic DILI usually has a delayed onset, encephalopathy usually appearing 26 weeks after jaundice (10). This is an important point that allows the clinician to predict patients at ALF risk when they are initially assessed.

Based on this concept, Robles-Diaz *et al.* (9) have proposed a new-R ratio (nR) [ $BT > 2$  mg/dL and  $(ALT/ULN)/(ALP/ULN) > 5$ , ALT is substituted by AST when the latter is higher] of a modified Hy's law at the first blood test available after presentation aiming to improve the definition of Hy's Law in terms of ALF prediction. It is important to emphasize that both nR criteria and the algorithm proposed by these authors are mainly useful during the early phases of DILI while they are less applicable when clinical symptoms have already appeared and the coagulation parameters indicate liver failure. A total of 282 cases from Spanish DILI Registry database which fulfilled the nR criteria at presentation were studied, including 27 ALF cases resulting in death or liver transplantation at DILI recognition (90% sensitivity and 63% specificity). This means that patients who would develop ALF are 2.43 times more likely to have positive tests (i.e., to fulfill the nR criteria) than individuals who would not develop ALF. Moreover, the chance of having a negative test for patients progressing to ALF is 0.16 times (i.e., approx. 1/6) of those who do not develop ALF. In order to further examine the applicability of the new definition of Hy's Law and the recently developed ALF algorithm proposed by Robles-Diaz *et al.* (9), they validated these algorithms in an independent series of Latin American DILI cases. This cohort from the Latin American DILI network (11) also included DILI cases induced by drugs

in the postmarketing arena (12). Ninety-seven DILI cases were analyzed, included 5 ALF/OLT cases. When applying the ALT criteria to define Hy's Law for ALF prediction, 55 cases fulfilled these criteria, including those who developed ALF, displaying 100% sensitivity and 45.7% specificity. However, when the new ALF algorithm was applied to the prediction of 20 cases with increased risk of developing ALF/OLT the ALF algorithm showed 80% sensitivity and 82% specificity. Similar results were also documented when this ALF algorithm was applied to the Spanish DILI Registry Cohort.

When the new algorithm to predict ALF was applied to patients from DILIN network, an incremental improvement in favor of nR modified Hy's law, with higher positive predictive value for overall fatality (14% *vs.* 10%) as well as a stronger independent association with DILI fatalities within 26 weeks was obtained, compared with the original algorithm (3). The difference primarily lies in the capability to predict those who would die of DILI related to ALF: 79% of ALF fatalities met nR Hy's law, whereas only 52% met the original Hy's law.

Interestingly, in the same analysis, MELD score obtained before 26 weeks was a better predictor of acute DILI deaths, when compared to Hy's law or nR Hy's law for ALF and ACLF

One major conclusion of this study is that the use of nR Hy's law is preferred over the traditional Hy's law as a predictor of increased risk of fatality at the early stages of DILI recognition and might be warranted in the post marketing clinical practice. More prospective data on DILI and ALF are needed to definitively confirm this assumption particularly during drug development.

Finally, two interesting points deserve a separate comment:

First, preexisting chronic liver disease was not associated in this study with mortality on multivariate analysis, though it was so on univariate one, in agreement with two other studies (13,14). However, the definition of severity of prior chronic liver disease did not openly specify neither fibrosis stage nor liver dysfunction.

Other variables, such as a higher international normalized ratio (INR), serum bilirubin and a lower albumin level reflected severe liver dysfunction in this study. In accordance with a recent analysis carried out by Stravitz *et al.* (15), a higher mortality and poor outcome was also observed in patients with ALF and low platelets.

Second, DILI contributed to death by worsening a preexisting liver disease (20%) or by contributing to a

non-liver-related death, such as DRESS/Steven-Johnson syndrome, sepsis, and malignancy (20% each). Many of these deaths occurred after DILI had resolved. DILI also significantly limited chemotherapy options in patients with cancer. This last issue also highlights the importance of carrying out studies analyzing fatal cases induced by DILI.

Regarding the long-term outcome of DILI diseases, the clinicians should keep in mind one important question to be answered in the future: Might biomarkers help us define subcategories among patients who meet the Hy's law criteria?

In the mean time the use of traditional DILI biomarkers associated with improved prognosis such as the refined Hy's law have an important bearing to aid treatment stratification and identify the risk factor for DILI outcome.

The development of DILI guidelines, expert meetings to carry out computer-based algorithms, the stimulation of a close dialog between different registries, and the design of prospective DILI studies assessing long-term outcomes will surely guide the progress in DILI management, to cope with difficult clinical scenarios.

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### Footnote

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