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Use of Hy's Law and a New Composite Algorithm to Predict Acute Liver Failure in Patients With Drug-Induced Liver Injury

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BACKGROUND & AIMS: Hy's Law, which states that hepatocellular drug-induced liver injury (DILI) with jaundice indicates a serious reaction, is used widely to determine risk for acute liver failure (ALF). We aimed to optimize the definition of Hy's Law and to develop a model for predicting ALF in patients with DILI. **METHODS:** We collected data from 771 patients with DILI (805 episodes) from the Spanish DILI registry, from April 1994 through August 2012. We analyzed data collected at DILI recognition and at the time of peak levels of alanine aminotransferase (ALT) and total bilirubin (TBL). **RESULTS:** Of the 771 patients with DILI, 32 developed ALF. Hepatocellular injury, female sex, high levels of TBL, and a high ratio of aspartate aminotransferase (AST):ALT were independent risk factors for ALF. We compared 3 ways to use Hy's Law to predict which patients would develop ALF; all included TBL greater than 2-fold the upper limit of normal (×ULN) and either ALT level greater than 3 × ULN, a ratio (R) value (ALT × ULN/ alkaline phosphatase × ULN) of 5 or greater, or a new ratio (nR) value (ALT or AST, whichever produced the highest ×ULN/ alkaline phosphatase × ULN value) of 5 or greater. At recognition of DILI, the R- and nR-based models identified patients who developed ALF with 67% and 63% specificity, respectively, whereas use of only ALT level identified them with 44% specificity. However, the level of ALT and the nR model each identified patients who developed ALF with 90% sensitivity, whereas the R criteria identified them with 83% sensitivity. An equal number of patients who did and did not develop ALF had alkaline phosphatase levels greater than 2 × ULN. An algorithm based on AST level greater than 17.3 × ULN, TBL greater than 6.6 × ULN, and AST:ALT greater than 1.5 identified patients who developed ALF with 82% specificity and 80% sensitivity. **CONCLUSIONS:** When applied at DILI recognition, the nR criteria for Hy's Law provides the best balance of sensitivity and specificity whereas our new composite algorithm provides additional specificity in predicting the ultimate development of ALF.

Keywords: Idiosyncratic Hepatotoxicity; Prognostic Risk Factor; Prediction; Progression.

Drug-induced liver injury (DILI) is a challenge for clinicians, the pharmaceutical industry, and regulatory agencies.[1] Furthermore, acute DILI has been reported to occur in 5%–10% of patients hospitalized for jaundice,[2] and more

Abbreviations used in this paper: **ALF, acute liver failure; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUROC, area under receiver operating characteristic curve; DILI, drug-induced liver injury; INR, international normalized ratio; LR, likelihood ratio; nR, new ratio; OLT, orthotopic liver transplantation; R, ratio; ROC, receiver operating characteristic; TBL, total bilirubin; ULN, upper limit of normal.**

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often evolves to fulminant hepatic failure than other causes of acute hepatic injury in Western countries.[3,4] Idiosyncratic hepatotoxicity was the presumptive cause in 13%–15% of cases of acute liver failure in reports from the United States and Sweden.[3,4] The spontaneous survival for patients with acute liver failure owing to idiosyncratic drug reactions is usually poor, with 60%–80% mortality without liver transplantation.[5,6]

In the late 1960s, Hyman Zimmerman,[7] the pioneer of modern hepatotoxicology, observed that the combination of jaundice and drug-induced hepatocellular injury was associated with a 10%–50% fatality rate from liver failure (before liver transplantations were performed), provided that other causes for increased bilirubin levels were excluded (hemolysis, Gilbert syndrome, and a major component of cholestasis). Analyses of large numbers of patients with suspected DILI from independent groups have validated these observations, showing 11.7% mortality/liver transplantation in patients with hepatocellular DILI and jaundice in the Spanish DILI Registry[8] and 12.7% in the Swedish Adverse Drug Reactions Advisory Committee retrospective database.[9]

Zimmerman's observation that hepatocellular DILI with jaundice indicates a serious reaction has been referred to as "Hy's Law."[10] Hy's Law cases have been defined more recently as drug-induced liver injury resulting in increased alanine aminotransferase (ALT) levels greater than 3 × the upper limit of normal (ULN) and total bilirubin (TBL) levels greater than 2 × the ULN after excluding other potential causes. This definition has been used by the US Food and Drug Administration over the years to identify drugs potentially capable of causing severe liver injury in the setting of clinical drug development.[1] To exclude cholestatic or mixed cases, the guidance for clinical trials states that for a Hy's Law case the liver injury should not have a significant alkaline phosphatase (ALP) increase reflecting a cholestatic component.[1] However, the definition of a significant cholestatic component is not precisely outlined.[11] An alternative approach to the definition of Hy's Law is to apply the ratio (R) value (ALT × ULN/ALP × ULN) to select hepatocellular cases rather than focusing only on ALT increases because it is assumed that there is much less risk of acute liver failure in cholestatic cases.

Although Hy's Law is based on Zimmerman's[7] clinical observations, its main use today is as a hepatotoxicity indicator in drug development. Nevertheless, Hy's Law also can provide a risk estimation of ALF progression in DILI cases induced by already marketed drugs. The use in this setting, however, is limited by its low specificity. The presence of a more specific algorithm/scale for physicians to predict potential ALF outcomes in established DILI cases could improve the clinical care for these patients.

In the present study we used the Spanish DILI Registry database in search of the best way to identify DILI patients who ultimately progressed to ALF and therefore can be viewed as true Hy's law cases because they developed ALF. We aimed to analyze whether the R value as well as a new ratio (nR) value, in conjunction with total TBL, provide a better way of identifying Hy's Law cases for ALF prediction than the widely used definition of Hy's Law based on ALT increases and whether ALP increases greater than 2-fold indicate cholestatic predominance sufficient to decrease the risk of acute liver failure/orthotopic liver transplantation (ALF/OLT). Once we optimized the standard approach to defining Hy's Law we recognized that there remained room for improvement in specificity. Therefore, we developed a composite statistical model with increased specificity to better predict an unfavorable outcome in patients with DILI in the clinical setting.

Patients and Methods

The study cohort encompassed all patients with idiosyncratic drug-induced liver injury entered into the Spanish DILI Registry since its foundation in April 1994 until August 2012. This prospective database contains detailed demographic, clinical, laboratory, imaging, and histologic (when available) information both at presentation and at follow-up evaluation of the patients included. Each case included in the study was evaluated by a clinician and remitted to the coordinating center where it was re-evaluated by a panel of DILI experts before being included in the database. A structured report form was used to record patient data, including details relating to: (1) the time lapse between the initial intake of the medication and the onset of liver disease and between the discontinuation of the suspected agent and improvement in, or recovery from, liver dysfunction; (2) serology and specific biochemistry to rule out viral hepatitis, autoimmune and metabolic liver disorders, appropriate imaging tests to exclude biliary disease, and any other alternative causes of liver injury; and (3) the outcome of the liver damage. Only cases considered as being drug-related (with the drug as the most likely cause) according to expert clinical judgment then were assessed using the Council for International Organizations of Medical Sciences scale, and only when the cases were classified as highly probable (42%), probable (49%), or possible (9%) were the data incorporated into the database. The criteria for DILI initially were those established by the Council for International Organizations of Medical Sciences (ALT level $>$ 2 × ULN, direct bilirubin level greater than 2 × ULN, or combined increases in ALT, aspartate aminotransferase (AST), and total bilirubin levels provided one of them is $>$2 × ULN)[12] and later restricted to the consensus criteria adopted in 2011 (ALT level $\geq$5 × ULN, ALP level $\geq$2 × ULN, or ALT level $\geq$3 ×ULN + TBL level $\geq$2 × ULN).[13] The pattern of liver injury was classified based on R values (ALT level × ULN/ALP × ULN).[13] A case was considered hepatocellular when R was 5 or greater, cholestatic when R was 2 or less, and mixed when the R value was between 2 and 5, using values from the first available blood analysis after DILI recognition.

The study cohort included 771 DILI patients. Of these, 738 experienced a single DILI episode, 32 had 2 DILI episodes, and 1 patient experienced 3 DILI episodes. Hence, a total of 805 DILI episodes were analyzed, of which 32 led to ALF/OLT. The definition of ALF used in this study was hepatic encephalopathy and coagulopathy (international normalized ratio [INR] $>$ 1.5) as reported by Møller et al.[14] The comparison of demographic parameters was based on available information from the 771 patients. Clinical and analytical parameter analyses were performed using available information corresponding to the 805 episodes at 3 different time points: DILI recognition, peak of ALT level, and peak of TBL level. All percentages were calculated based on the total number of available patient or episode data. For ALF case 31 (Supplementary Table 1), which occurred after accidental re-challenge, no laboratory information could