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CLINICAL—LIVER

Idiosyncratic Drug-Induced Liver Injury Is Associated With Substantial Morbidity and Mortality Within 6 Months From Onset

Robert J. Fontana,[1] Paul H. Hayashi,[2] Jiezhun Gu,[3] K. Rajender Reddy,[4] Huiman Barnhart,[3] Paul B. Watkins,[2] Jose Serrano,[5] William M. Lee,[6] Naga Chalasani,[7] Andrew Stolz,[8] Timothy Davern,[9] and Jayant A. Talwakar,[10] on behalf of the DILIN Network

[1]*Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan;* [2]*University of North Carolina, Chapel Hill, North Carolina;* [3]*Duke Clinical Research Institute, Durham, North Carolina;* [4]*Division of Gastroenterology and Hepatology, University of Pennsylvania, Philadelphia, Pennsylvania;* [5]*Liver Disease Research Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland;* [6]*Division of Digestive and Liver Diseases, University of Texas Southwestern Medical Center, Dallas, Texas;* [7]*Department of Medicine, Indiana University, Indianapolis, Indiana;* [8]*University of Southern California, Los Angeles, California;* [9]*California Pacific Medical Center, San Francisco, California; and* [10]*Mayo Clinic, Rochester, Minnesota*

This article has an accompanying continuing medical education activity on page e19. Learning Objective: Upon completion of this CME activity, successful learners will be able to identify the incidence and risk factors for early death/ liver transplantation as well as evolution to chronic liver injury in patients presenting with drug induced liver injury.

Podcast interview: www.gastro.org/gastropodcast. Also available on iTunes.
See Covering the Cover synopsis on page 1; see editorial on page 20.

BACKGROUND & AIMS: Little is known about the incidence of drug-induced liver injury (DILI) and risk factors for adverse outcomes. We evaluated short-term outcomes of a large cohort of patients with DILI enrolled in an ongoing multicenter prospective study. **METHODS:** Data were collected from 660 adults with definite, highly likely, or probable DILI. Regression methods were used to identify risk factors for early liver-related death or liver transplantation and chronic liver injury. **RESULTS:** Patients' median age was 51.4 years; 59.5% were female and 59.1% required hospitalization. Within 6 months of DILI onset, 30 patients received liver transplants (4.5%; 95% confidence interval [CI], 3.0%–6.1%) and 32 died (5%; 95% CI, 3.2%–6.5%); 53% of the deaths were liver related. Asian race, absence of itching, lung disease, low serum albumin levels, low platelet counts, and high serum levels of alanine aminotransferase and total bilirubin at presentation were independent risk factors for reduced times to liver-related death or liver transplantation (C-statistic = 0.87). At 6 months after DILI onset, 18.9% of the 598 evaluable subjects had persistent liver damage. African-American race, higher serum levels of alkaline phosphatase, and prior heart disease or malignancy requiring treatment were independent risk factors for chronic DILI (C-statistic = 0.71). **CONCLUSIONS:** Nearly 1 in 10 patients die or undergo liver transplantation within 6 months of DILI onset and nearly 1 in 5 of the remaining patients have evidence of persistent liver injury at 6 months. The profile of liver injury at presentation, initial severity, patient's race, and medical comorbidities are important determinants of the likelihood of death/transplantation or persistent liver injury within 6 months.

Keywords: Hepatotoxicity; Acute Liver Failure; Transplantation; Causality.

Drug-induced liver injury (DILI) is an infrequent cause of liver disease in the general population and accounts for <1% of hospitalized patients presenting with jaundice.[1,2] Nonetheless, DILI is a leading reason for regulatory actions involving investigational and approved medications and is also a leading cause of acute liver failure in the United States.[3,4] Because of its low incidence and the difficulty in establishing a diagnosis, the natural history of DILI is not well described. One frequently cited report suggested that prolonged medication administration and inadvertent drug rechallenge might be risk factors for developing chronic DILI.[5] In addition, DILI patients with cholestatic liver injury might have a slower rate of biochemical improvement and be at increased risk for developing chronic liver disease.[6,7] However, the number of patients reported in earlier studies was limited and variable criteria for chronic DILI were used.[6–8]

The Drug-Induced Liver Injury Network (DILIN) consists of 8 academic medical centers and a data-coordinating center sponsored by the National Institutes of Health. In 2004, a prospective registry study of patients with suspected DILI was initiated to improve our understanding of the etiology, risk factors, and natural history of DILI in the United States.[8,9] Subjects with liver injury that persists for at least 6 months

Abbreviations used in this paper: **ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; CI, confidence interval; DILI, drug-induced liver injury; DILIN, Drug-Induced Liver Injury Network; HDS, herbal and dietary supplement; INH, isoniazid; INR, international normalized ratio; ULN, upper limit of normal.**

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after DILI onset are followed for 2 years to better define their long-term outcomes. In the initial analysis of the first 300 patients enrolled in the DILIN database, 15% of the subjects met predefined laboratory, clinical, and/or radiographic criteria for chronic DILI at 6 months after presentation.[10] In the current analysis, we set out to determine the short-term (6 month) rates of death, liver transplantation, and chronic DILI of the first 660 evaluable adult patients enrolled in the DILIN prospective study with definite, highly likely, or probable DILI. In addition, we set out to identify risk factors at presentation for early death or liver transplantation as well as for self-limited vs chronic DILI.

Methods

Drug-Induced Liver Injury Network Prospective Study

The protocol for this multicenter observational study was approved by the Institutional Review Boards at each clinical site and all enrolled subjects provided written informed consent. DILI onset was defined as the first date after a subject taking any medication or herbal and dietary supplement (HDS) met the predefined laboratory criteria for study entry. Specifically, all subjects had to have a serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) level that exceeded 5× the upper limit of normal (ULN) (or 5× pretreatment baseline if baseline abnormal), a serum alkaline phosphatase (ALP) that exceeded 2× the ULN (or 2× pretreatment baseline if baseline abnormal), a total bilirubin >2.5 mg/dL, or an international normalized ratio (INR) >1.5 on 2 consecutive blood draws. All study participants were older than 2 years of age and had to be enrolled within 6 months of DILI onset. Patients with known or suspected acetaminophen hepatotoxicity, autoimmune hepatitis, or primary sclerosing cholangitis, or a history of a bone marrow or liver transplantation before DILI onset were excluded.

A detailed medical and medication history was obtained at the baseline study visit and additional laboratory and radiologic testing was performed to more fully characterize the DILI event and exclude competing etiologies. All enrolled patients were seen for a follow-up study visit at 6 months after initial enrollment and those with evidence of chronic DILI within 6 months of DILI onset were asked to return for additional follow-up visits at 12 and 24 months. Chronic DILI was defined as having a persistently elevated serum AST, ALT, ALP, or total bilirubin level, histologic evidence of ongoing liver injury, or radiologic evidence of persistent liver injury (ie, ascites on imaging) at 6 months or more after the initial DILI onset date.[9,10] The causal relationship between the liver injury episode and the implicated agent(s) was evaluated in a standardized fashion by the DILIN causality committee.[11] A DILIN causality score varying from 1 (Definite >95% likelihood), 2 (Very Likely 75%–95% likelihood), 3 (Probable 50%–74% likelihood), 4 (Possible 25%–49% likelihood), to 5 (unlikely <25% likelihood) was assigned by consensus agreement of committee members. In subjects with 2 or more implicated drugs, an overall causality score was assigned to the case and then an individual causality score for each drug was given. For cases with multiple implicated HDS products (with or without implicated drugs), an overall causality score was assigned to the case and then a causality score for each individual drug and one overall HDS causality score for all HDS products was assigned. Only the overall causality score for the case was used for reporting. A primary implicated agent was assigned to each case as the agent with the highest individual causality score or the one with higher ranking by site if ties occur. A 3-tiered nested system was used in DILIN to classify the primary implicated agents into primary (overall class), secondary (based on use), and tertiary (based on chemical class). In addition, the severity of the DILI episode was categorized on a 5-point scale from mild (1), moderate (2), moderate-hospitalized (3), severe (4), and fatal (5), where a fatal score was assigned only if the patient died or had liver transplantation due to DILI. Before April 2009, causality was assessed from baseline data and a clinical narrative. After April 16, 2009, accrued 6-month follow-up data were included in the causality assessment, which involves 485 of the 660 patients in this study. All deaths in DILIN patients were classified by clinical site as liver-related or not. The enrolled cases with an overall causality score of "possible" (4) or "unlikely" (5) or not adjudicated yet were excluded from the current analysis, as were children (n = 36). To identify predictors of chronic liver injury, subjects with known pre-existing chronic hepatitis B virus/hepatitis C virus (n = 28) were also excluded from this analysis, as were subjects whose chronic status could not be determined due to dropping out of study before completing their 6-month study visit (n = 77).

Statistical Methods

Descriptive statistics, mean with SD or median with range, were used to describe continuous variables, and frequency and percent were used to describe categorical variables. A nonparametric test, Wilcoxon or Kruskal-Wallis test, was used for comparison of 2 or 3 groups for continuous variables, and χ^2 test for comparison between groups for categorical variables. Data for early outcomes (non–liver-related death, liver-related death, or liver transplantation) within 6 months of DILI onset were first described and modeled. Then, data for chronic status at 6 months after DILI onset were described and modeled. Demographic and clinical data at DILI onset or between onset and 6 months from onset were extracted to describe and compare 2 groups with and without 2 early outcomes of interest: death or transplantation within 6 months and chronic DILI at 6 months after DILI onset. Death was subcategorized as liver or non–liver-related and descriptive statistics were used to describe and compare the 3 early adverse events: liver transplantation, liver-related death, and non–liver-related death. Cox regression hazard models were used for time to early event analyses where an early event is defined as death or liver transplantation within 6 month of onset. Clinically, it makes more sense to consider only liver-related early event, rather than lumping all death and liver transplantations together. Time to early liver-related event (liver-related death or liver transplantation) was also performed. Logistic regression was used to model the binary outcomes of chronic status. All model selection used an initial univariate analysis to screen potential candidates for multivariate modeling. Variables with a univariate P value $\leq$.1 were considered. For variables with known co-linearity or high correlation, clinical judgment was used to select one predictor for additional modeling, for example, jaundice and total bilirubin are highly related and only total bilirubin was used in the multivariate modeling due to its clinical objectivity. Stepwise selection