HHS Public Access

Author manuscript

Gastroenterology. Author manuscript; available in PMC 2016 June 01.

Published in final edited form as:

Gastroenterology. 2015 June ; 148(7): 1340–1352.e7. doi:10.1053/j.gastro.2015.03.006.

Features and Outcomes of 899 Patients with Drug-induced Liver Injury: The DILIN Prospective Study

N Chalasani[1], **HL Bonkovsky**[2], **R Fontana**[3], **W Lee**[4], **A Stolz**[5], **J Talwalkar**[6], **KR Reddy**[7], **PB Watkins**[8], **V Navarro**[9], **H Barnhart**[10], **J Gu**[10], **J Serrano**[11], and **for the United States Drug Induced Liver Injury Network**

[1]Indiana University School of Medicine, Indianapolis, IN

[2]Carolinas Health Care System, Charlotte, NC

[3]University of Michigan, Ann Arbor, MI

[4]University of Texas at Southwestern, Dallas, TX

[5]University of Southern California, Los Angeles, CA

[6]Mayo Clinic, Rochester, MN

[7]University of Pennsylvania, Philadelphia, PA

[8]University of North Carolina, Chapel Hill, NC

[9]Einstein Medical Center, Philadelphia, PA

[10]Duke Clinical Research Institute, Raleigh, NC

[11]National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD

Abstract

Background & Aims—The drug-induced liver injury network (DILIN) is conducting a prospective study of patients with DILI in the United States. We present characteristics and subgroup analyses from the first 1257 patients enrolled in the study.

Methods—In an observational longitudinal study, we began collecting data on eligible individuals with suspected DILI in 2004, following them for 6 months or longer. Subjects were evaluated systematically for other etiologies, causes, and severity of DILI.

Results—Among 1257 enrolled subjects with suspected DILI, the causality was assessed in 1091 patients, and 899 were considered to have definite, highly likely, or probable DILI. Ten percent of

Author for Correspondence Naga Chalasani, MD, FACG, David W. Crabb Professor& Director, Division of Gastroenterology and Hepatology, Indiana University School of Medicine, 1050 Wishard Boulevard, RG 4100, Indianapolis, IN 46202, Tel (317) 278-0414, Fax (317) 278-1949, nchalasa@iu.edu.

Investigators with an outside interest with a particular pharmaceutical company were not assigned cases for adjudication when the implicated agent was manufactured by the same company.

patients died or underwent liver transplantation and 17% had chronic liver injury. In the 89 patients (10%) with pre-existing liver disease, DILI appeared to be more severe than in those without (difference not statistically significant; *P*=.09) and mortality was significantly higher (16% vs 5.2%; *P*<.001). Azithromycin was the implicated agent in a higher proportion of patients with pre-existing liver disease compared to those without liver disease (6.7% vs. 1.5%, p=0.006). Forty-one cases with latency ≤ 7 days were caused predominantly by antimicrobial agents (71%). Two most common causes for 60 DILI cases with latency >365 days were nitrofurantoin (25%) or minocycline (17%). There were no differences in outcomes of patients with short vs long latency of DILI. Compared to individuals younger than 65 y, individuals 65 y or older (n=149) were more likely to have cholestatic injury, although mortality and rate of liver transplantation did not differ. Nine patients (1%) had concomitant severe skin reactions; implicated agents were lamotrigine, azithromycin, carbamazepine, moxifloxacin, cephalexin, diclofenac, and nitrofurantoin. Four of these patients died.

Conclusion—Mortality from DILI is significantly higher in individuals with pre-existing liver disease or concomitant severe skin reactions compared to patients without. Further studies are needed to confirm the association between azithromycin and increased DILI in patients with chronic liver disease. Older age and short or long latencies are not associated with DILI mortality.

Keywords

DILI; DILIN; Hepatotoxicity; Chronic DILI; Idiosyncratic; toxicity; medication

INTRODUCTION

Idiosyncratic drug induced liver injury (DILI) is a rare clinical event but it carries significant morbidity and mortality (1–3). Its annual incidence in the general population ranges between 14 and 19 events per 100,000 inhabitants with nearly 30% exhibiting jaundice (4, 5). It is one of the leading causes of acute liver failure in the United States (6, 7) and it continues to be an important barrier for new drug development and marketing (8). The Drug Induced Liver Injury Network (DILIN), funded by the U.S. National Institutes of Health, is a consortium of several academic institutions and its overarching goal is to comprehensively investigate all aspects of DILI in both children and adults (9). The DILIN Prospective Study is an ongoing undertaking of the DILIN. It is an observational longitudinal study of individuals ≥ 2 years of age with suspected DILI (10). Initiated in 2004, this study has led to several publications related to DILI (11–15), including a summary of its initial 300 participants enrolled. The main findings of those studies were (a) antimicrobials and herbal or dietary supplements (HDS) were the major causes, (b) acute DILI carried an 8% risk of mortality and 13% risk of unresolved or chronic injury at 6 months following onset, and (C) acute hepatitis C and E can masquerade as DILI. Since that report, the DILIN Prospective Study has continued to enroll subjects, providing an opportunity to further characterize DILI in the United States in a large cohort of patients who were carefully followed and assessed in a standardized fashion.

The main objectives of this paper are to provide (a) summary description of subjects enrolled and their outcomes, (b) more detailed description and characterization of DILI caused by major therapeutic classes and individual agents in the United States, and (c)

several notable aspects of DILI: like DILI in individuals with preexisting liver disease, in older persons, with short and very long latency, and associated with severe cutaneous reactions.

METHODS

A detailed description of the DILIN's enrollment and case ascertainment procedures has been published elsewhere (10). Briefly, subjects considered for enrollment into the DILIN sign a written informed consent approved by the local institutional review board. Subjects are at least 2 years of age at the time of enrollment, and suspected of having experienced potential non-acetaminophen DILI within the preceding six months. Criteria for enrollment included jaundice (serum bilirubin ≥ 2.5 mg/dL) or coagulopathy (INR > 1.5) with any elevations in alanine or aspartate aminotransferase (ALT or AST) alkaline phosphatase (Alk P) levels; or, in the absence of jaundice or coagulopathy, elevations of ALT or AST above 5 times the upper limit of normal (ULN) or Alk P above 2 times ULN. The point at which these eligibility criteria were met was used as the definition of onset of hepatotoxicity (as opposed to time of onset of symptoms). At the baseline visit, study subjects were queried on the chronological use of all drugs and HDS. In addition, relevant clinical, biochemical, serological, imaging, and histological data were abstracted from the medical record and, if not already done, testing was performed for conditions that can mimic DILI, including serology for hepatitis A, B, C and E, CMV, EBV, HSV, and for autoimmune hepatitis. Subjects were asked to return for repeated testing at six months; if the serum chemistry values or hepatic imaging or examination remained abnormal at that time, the injury was regarded chronic, and follow-up was continued with visits at months 12 and 24. This information was assembled into a pre-defined dataset for the causality assessment process. It should be noted that some of the subjects included in this paper have been included in previous papers published by the DILIN. The liver histology findings from most of the patients contained in this paper who had a liver biopsy during their liver injury episode have been previously described (14) and thus are not included in this report.

Severity Assessment

Laboratory and clinical data were used to assign a disease severity score. Severity was scored as mild (1+) for serum enzyme elevations in the absence of jaundice (bilirubin < 2.5 mg/dL); moderate (2+) by jaundice (bilirubin ≥ 2.5 mg/dL) or coagulopathy (INR >1.5) without the need for hospitalization; moderately severe (3+) by jaundice or coagulopathy and need for hospitalization; severe (4+) by jaundice and signs of hepatic or other organ failure; and fatal (5+) by death from liver disease or the need for liver transplantation within six months of onset.

Causality Assessment

The causal relationship between the liver injury and the implicated drug or HDS was evaluated in a formal and standardized fashion by the DILIN Causality Committee as previously described (10). Causality was assessed as either definite (>95% likelihood), highly likely (75–95%), probable (50–74%), possible (25–49%) or unlikely (<25%). In cases in which several agents were considered possibly implicated, the overall event was

adjudicated for the likelihood that it was DILI, and then each agent was given a separate score, but only one agent was permitted to be considered as being highly likely or definitely responsible. Cases involving HDS products were often complex, in that multiple products were used and the components in the products were often varied and their concentration and nature were not always well defined. For this reason, HDS products (even when several were being taken) were adjudicated as a single agent at the time of this manuscript preparation. Agreement among the reviewers was achieved through email communications and teleconferences. Only cases of confirmed DILI (i.e. probable, highly likely or definite) were included in this report. The causality assessment for each case occurred 6 months after their enrollment which provided an opportunity to follow each case wherever possible for 6 months and this permitted better characterization of the relationship between the implicated agent and the liver injury event.

Assessment of Clinical Patterns of Liver Injury

Assessing the pattern of liver injury as hepatocellular, cholestatic, or mixed is based on calculating the “R” ratio, defined by the ratio of serum ALT to Alk P, both expressed as multiples of the ULN. By convention, an R ratio of >5 indicates hepatocellular, <2 cholestatic, and 2–5 mixed injury (16, 17). The R ratio applied to each case was calculated based upon values at the onset of injury. In this study we also evaluated a modified R-ratio which was based on peak serum ALT and Alk P values, rather than their values at presentation.

Data Management and Statistical Analyses

Demographic and clinical data for subjects enrolled into the DILIN Prospective Study between September 2004 and May 2013 were extracted on May 16, 2013. Descriptive statistics such as means with standard deviation, median with interquartile ratios and frequency distributions were used to describe the cohort. Between group difference were tested using the chi-square test for categorical variables and Wilcoxon/Kruskal-Wallis test for the continuous variables. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Inc, Cary, NC). A p-value <0.05 was considered statistically significant.

RESULTS

Summary Description of Subjects Enrolled and their Outcomes

Between September 1, 2004 and May 16, 2013, 1257 subjects were enrolled into the DILIN Prospective Study. Among these, 1091 had been reviewed and adjudicated by a panel of expert hepatologists at the time of these analyses. The scores for likelihood of causality were definite in 235 (22%); highly likely in 466 (43%), probable in 198 (18%), possible in 142 (13%) and unlikely in 50 (5%). The common etiologies for liver injury among these 50 cases deemed as unlikely due to DILI are flare up of underlying liver disease due to hepatitis B or C, autoimmune hepatitis, unsuspected biliary obstruction, and multifactorial (e.g., multiple medication, sepsis, and transfusions), especially in those who were hospitalized. This analysis is limited to the 899 subjects with causality scores of definite, highly likely, or probable.

Among the 899 subjects with confirmed DILI, 56 (6%) died within 6 months of onset of whom 27 (48%) were considered to have died from liver failure related to the drug-induced injury. An additional 33 patients underwent liver transplantation (4%) within six months of onset. Thus, 10% of the subjects had a fatal outcome that was considered related to the DILI event. And additional 126 [17.5%] subjects had evidence of continuing liver injury after 6 months [subsequently termed “chronic DILI”]. Thus, almost a quarter of patients with DILI either died, underwent liver transplant or had residual liver injury at the time of six month follow up after onset.

Demographic and selected clinical information for the 899 subjects studied—comparisons by their pattern of liver injury

As shown in Table 1, the pattern of liver injury was hepatocellular in 54%, and cholestatic or mixed in 23% each. Patients with hepatocellular DILI tended to be younger ($p < 0.001$), less likely to be clinically jaundiced, and to have higher ALT levels than patients with cholestatic or mixed injury. In addition, women were relatively over-represented in the hepatocellular cohort (65%) compared to the cholestatic or mixed group (51%). The so-called ‘latency’, that is the time from start of the implicated drug to the time of identification of abnormality laboratory tests was significantly longer in hepatocellular cases (median = 46 vs 31 days, $p < 0.001$). Immuno-allergic features (at least two of the three features of fever, rash, or absolute eosinophilia>500μL) were more frequent in cholestatic (16%) and mixed injury (18%) than hepatocellular cases (11%).

The time course of injury was significantly more protracted in cholestatic than in the mixed or hepatocellular cases. The distribution of DILI severity scores was dichotomous, in that hepatocellular cases had higher proportions that were mild (ALT elevations without jaundice) but also a higher frequency of fatal cases (liver related death or transplantation) than cases with the cholestatic or mixed injury patterns. Strikingly, patients classified as having mixed injury had milder disease overall with fewer liver-related deaths and no cases undergoing liver transplantation. While 18% of all patients had evidence of chronic or unresolved injury six months after onset (chronic DILI), this outcome was much more frequent among cholestatic cases (31%) than either hepatocellular (13%) or mixed-injury cases (14%). Thus, the pattern of liver injury at the onset of the clinical syndrome had implications for disease severity and outcome with hepatocellular cases more likely to be fatal but cholestatic cases more likely to be prolonged and result in chronic injury. Cases of mixed injury had the most favorable prognosis and outcomes.

Most frequently implicated classes of drugs and most frequently implicated individual drugs

The 899 cases were ultimately attributed to one or more of 190 different agents, including 145 due to HDS and 754 due to prescription drugs. A total of 189 prescription drugs were primary implicated agents for these 754 cases (Supplementary table 1). Antimicrobials were by far the most common class of causative drugs, accounting for 408 [45%] instances (Table 2). Indeed, among individual agents, the nine most commonly implicated agents were all antimicrobials, mostly antibiotics (Table 2). Of importance, herbal agents/dietary supplements [HDS] were the second most common group but only rare specific HDS agents

were implicated more than once and none were in the top 25 implicated agents (data not shown). Other therapeutic classes of agents included cardiovascular drugs (88: 10%), central nervous system agents (82: 9%), antineoplastic drugs (49: 5%) and analgesics (33: 3%, largely nonsteroidal anti-inflammatory agents). A more detailed analysis of the spectrum of HDS products that cause liver injury in this cohort as well as the secular trends in HDS-related liver injury is described in greater detail elsewhere (17). Between initiation of the DILIN Prospective Study in 2004 and the most recent years of accrual of patients, the proportion of cases attributed to HDS has risen from approximately 7% to 17%.

A listing of all prescription drugs that were implicated as either definite, highly likely or probable in at least one DILI case is given in Supplementary Table 1. The ten most commonly implicated non-HDS agents accounted for 25% of all cases and the 25 most common non-HDS agents accounted for half of all cases. The remaining half of cases were caused by agents implicated in only 1 or 2 cases. These results demonstrate the diversity of causes of DILI.

Comparisons among most frequent classes of agents and single agents

Among the five most frequent classes of prescription drugs (antimicrobials, cardiovascular agents, CNS agents, antineoplastic agents, analgesics), there were few clinical differences in the liver injury attributed to their use (Table 3). Most of the differences were attributable to differences in the types of patients who would receive these agents. Thus, those with liver injury from CNS agents were younger than subjects in the other cohorts (the major agents being anticonvulsants and antipsychotic medications). Not surprisingly, those with DILI due to anti-neoplastic agents were more likely to die within 12 months of onset and none underwent liver transplantation. Similarly, analyses of selected characteristics of DILI for the ten most frequent prescription drugs, also showed few notable differences (Supplemental Table 2). There were higher frequencies of increased eosinophil counts in DILI due to trimethoprim-sulfamethoxazole (31%), cefazolin (30%), ciprofloxacin (33%), all of which are known frequently to cause immuno-allergic liver injury (2). There also were higher frequencies of high-titer ANA positivity in nitrofurantoin (52%) and minocycline (57%)-induced DILI; both of these drugs are well known to trigger auto-immune hepatitis in susceptible persons (2). For other agents, ANA, when positive, had low titers and with frequencies similar to that observed in adult US population (18). DILI due to analgesics was usually hepatocellular in nature; for example all 12 cases of diclofenac DILI were hepatocellular. Among the cases of analgesic DILI, there was only one death and no one required liver transplantation.

Pattern of liver injury according to a modified definition

The R-ratio which biochemically characterizes DILI is typically defined based on ALT and Alk P values at the time of onset. However, some patients present with a hepatocellular pattern of injury, but subsequently developed marked cholestasis. We therefore sought to assess the significance of using an R-ratio based on the peak ALT and peak Alk P values, which are often non-concurrent. According to this modified R-ratio, the proportion of hepatocellular (52%), cholestatic (25%) and mixed DILI (23%) were largely unchanged. Furthermore, the clinical and biochemical characteristics and outcomes of hepatocellular,

cholestatic and mixed DILI were not different between two definitions of the R-ratio (data not shown). Using the modified R-ratio, 5 cholestatic cases were reclassified as hepatocellular, and 8 originally hepatocellular cases were reclassified as cholestatic.

Selected characteristics among the elderly (≥ 65 years) compared to younger subjects (< 65 years)

The demographic and clinical features of DILI were generally similar in older and younger participants (Table 4). The most striking differences were the higher proportion of cholestatic pattern of injury among the elderly (36% vs 21%, $p < 0.001$) with significantly higher levels of serum Alk P (at onset, mean, 410 vs 264; at peak 520 vs 383 U/L, p for both < 0.001). The severity of liver injury was somewhat lower in the elderly group (p=0.08) as was the frequency of chronic DILI (11% vs 19%, p =0.04).

Nine subjects with severe cutaneous adverse reactions

As summarized in Table 5, six subjects exhibited features of Stevens Johnson Syndrome (SJS) and 3 had toxic epidermal necrolysis (TEN) (1%). The implicated agents were lamotrigine (n=2), azithromycin (n=2), carbamazepine (n=1), moxifloxacin [1], cephalexin (n=1), diclofenac (n=1), and nitrofurantoin [1]. The pattern of liver injury was hepatocellular in 7 and mixed in 2 patients. In keeping with the known high severity of illness in SJS, four of the nine individuals died and an additional individual developed chronic injury, in a pattern suggestive of vanishing bile duct syndrome.

DILI in underlying liver disease

Eighty-nine [10%) subjects with DILI had known pre-existing chronic liver disease, mainly hepatitis C (n=36) and nonalcoholic fatty liver disease or unexplained elevations in liver biochemistries (n=47). Demographic and clinical features of this cohort were generally similar to those of patients without known underlying chronic liver disease (Table 6). There were no significant differences in the classes of agents to cause DILI in the pre-existing liver group (p=0.2) and the top 5 classes of agents were antimicrobials (51%), HDS (13.5%), cardiovascular agents (7%), antineoplastic agents (6%) and CNS agents (4.5%). A full listing of all implicated agents in individuals with underlying chronic liver disease is shown in Supplemental Table 3. Commonly implicated agents were isoniazid (n=7), azithromycin (n=6), amoxicillin-clavulanate (n=4) and nitrofurantoin (n=4). Interestingly, azithromycin was the implicated agent in a higher proportion of patients with pre-existing liver disease compared to those without liver disease (6.7% vs. 1.5%, p=0.006). Individuals with pre-existing liver disease also had a higher prevalence of diabetes [38% vs 23%, $p = 0.004$]. There was a trend for levels of serum ALT and Alk P to be lower in those with pre-existing liver disease, but serum total bilirubin and INR were not different. There were differences in the causality scores with fewer cases of definite DILI in individuals with pre-existing liver disease (p=0.009). Severity of the liver injury tended to be higher in those with pre-existing liver disease but this did not reach statistical significance (p=0.09). Importantly, there was higher mortality in those with pre-existing liver disease [16% vs 5.2%, $p < 0.001$].

Short (≤ 7 days) vs long latency DILI (> 365 days)

We examined whether there were differences between subjects and their clinical courses, depending upon the 'latency', the number of days between the start of the causative medication and onset of laboratory evidence of DILI (Table 7). There were 41 short-latency DILI cases (4.5%) and the most commonly implicated agents were moxifloxacin (n=4), azithromycin (n=3), ciprofloxacin (n=3), rifampin (n=2), and levofloxacin (n=2). However, there were 60 cases with long latency (6.7%) and the most commonly implicated agents were nitrofurantoin (n=16), minocycline (n=10), statins (n=4), amiodarone (n=3), mercaptopurine (n=3), atomoxetine (n=2), tamoxifen (n=2), oxaliplatin (n=2) and interferon-beta (n=2). The frequencies of different patterns of liver injury and profile of liver biochemistries were not different between the two groups. There were trends for slower resolution of DILI and a trend toward higher likelihood of chronic DILI in those with long latency (31% vs 12.5%, p= 0.07) but the rates of death or liver transplantation were not different.

DISCUSSION

The DILIN Prospective Study initiated in 2004 has resulted in several important papers published previously. These include the characteristics of initial 300 patients enrolled (11), natural history of DILI (15) liver histology of DILI (14), DILI in children (20), DILI caused by intravenous agents (21), and DILI caused by selected agents (e.g., duloxetine (22), flavocoxid (13), interferon-beta (23), quinolones(24). The current paper with by far the largest number of prospectively characterized cases of DILI reports several findings which have not been reported previously in the literature.

Some novel aspects of this report are description of DILI (a) in the elderly, (b) occurring in individuals with underlying chronic liver disease, (c) with very short and long latency, and (d) associated severe cutaneous reactions. In addition, it describes temporal trends in the causative agents of DILI over the last decade and also provides a detailed comparison of characteristics of DILI caused by most common therapeutic classes and individual agents.

Older age is not necessarily a risk factor for all-cause DILI but elderly individuals may be higher risk for DILI caused by specific compounds such as amoxicillin-clavulanate (25), isoniazid (26,27) and nitrofurantoin (28). Furthermore, it previously has been described that cholestatic DILI is more common in the elderly whereas younger individuals are more likely to present with hepatocellular DILI (29). This study consisting of a large number of individuals who are ≥ 65 years of age indeed confirms that the pattern of their liver injury is more likely to be cholestatic than in individuals who are < 65 years of age. It is unclear if there is a biological basis for such a difference in the phenotype or if it is a reflection of causative agents for DILI in the elderly. In fact, there is significantly highly representation of antimicrobials in the elderly individuals (57.5% vs. 43%, p=0.047) and antimicrobials such as amoxicillin-clavulanate are known to predominantly cause cholestatic DILI. Although there was more cholestatic DILI which is generally associated with higher likelihood of chronic DILI, the frequency of chronic DILI in the elderly in this cohort was significantly lower than in those who are < 65 years of age. This may in part be due to lower prevalence of DILI caused by anabolic steroids in the elderly group which are known to

cause prolonger cholestasis and higher likelihood of chronic DILI. Despite their older age and polypharmacy, elderly group did not have higher frequency of liver transplantation or death.

Some patients with DILI are known to present with severe cutaneous reactions such as SJS and TEN but its causative agents and clinical characteristics are not well defined. The 1% prevalence of SJS/TEN in this cohort is significantly lower than 7.7% prevalence in pediatric DILI reported from India (30). In this report from India, out of 39 children with DILI, three developed SJS/TEN due to phenytoin (n=2) and carbamazepine (n=1). Interestingly, there were no instances of SJS or TEN among 96 cases of DILI reportedly recently from Iceland (5) (*Personal communication, Prof. Einar Bjornsson, Reykjavik, Iceland*). In our experience, lamotrigine and azithromycin were the two common causes of DILI with severe skin adverse reactions, with a frequency of 22% for lamotrigine DILI (2 out of 9 definite/highly likely/probable lamotrigine DILI cases) and 11% for azithromycin DILI (2 out of 18 definite/highly likely/probably azithromycin DILI cases). Drugs commonly described as at risk for causing severe cutaneous drug reactions are nevirapine, lamotrigine, carbamapezine, phenytoin, phenobarbital, trimethoprim-sulfamethaxozole and another anti-infective sulfonamides, allopurinol, oxicam NSAIDs, aminopencillins, cephalosporins and quinolones (31). Mortality rate for SJS/TEN in our series was 44% with 3 out of 4 deaths occurring during the acute episode whereas one 10 year old child who developed bronchiolitis obliterans and died subsequently due to respiratory failure. The high mortality rate observed in this series is generally consistent with 25–30% mortality rate described for severe cutaneous adverse reactions (32).

It has been stated that patients with chronic liver disease and cirrhosis are not necessarily at risk for all-cause DILI, but it is likely that when an event of DILI occurs they may be at higher risk for adverse outcomes such as liver failure or death (33). However, a systematic evaluation of etiologic agents, clinical characteristics and outcomes of DILI in individuals with preexisting chronic liver disease has been lacking. We found no enrichment of any particular therapeutic class in the liver disease group but interestingly there was significant enrichment of azithromycin DILI in individuals with preexisting chronic liver disease. It is unclear if individuals with underlying liver disease are at higher risk for DILI due to azithromycin or this phenomenon is merely a reflection of its higher usage in this patient population due to its presumed safety. It is noteworthy that we did not find higher prevalence of INH DILI in the liver disease cohort (6.7% in liver disease vs 5.2% in the non-liver disease group, p=0.5) but this could reflect lower usage of INH in individuals with preexisting liver disease. Higher mortality rate noted in the liver disease group supports the existing dictum that DILI events in individuals with chronic liver disease leads to higher adverse outcomes.

It is noteworthy that individuals who were ≥ 65 years of age had significantly higher incidence of Hy's law and yet their mortality was not significantly different from those who were under 65 years ago. The reason for discrepancy is unclear but we observed a similar pattern with DILI suspected due to diclofenac where there was 42% incidence of Hy's law and yet there were no deaths attributable to liver injury. This raises the possibility that the

relationship between Hy's law and mortality due to hepatocellular DILI may depend on the compound implicated. More work is needed in this area to further clarify this issue.

There are many examples in the literature of instances of DILI occurring either with short (<7 days) or after long (>6–12 months) latency but a systematic evaluation of etiologic agents and characteristics of DILI with short and long latency has previously not been conducted. Contrary to our expectation, there was not significantly higher frequency of hypersensitivity features among DILI cases with short latency but 2 out of 9 DILI cases with SJS/TEN had short latency (Table 5). Although nitrofurantoin and minocycline are the two dominant causes of DILI with long latency, a number of other medications such as 6-mercaptopurine, statins and amiodarone are also associated with DILI after prolonged latency. The knowledge that sometimes DILI can occur after long latency may prevent the clinicians from missing a diagnosis of DILI with catastrophic consequences.

An observation that we made in our initial report in 2008 about relatively lower frequency of serious adverse outcomes in mixed DILI continues to hold true in this paper (11). The 5.4% frequency of death and transplantation in individuals with mixed DILI was lower than 11.6% and 11.9% frequency of death and transplantation in individuals with hepatocellular and cholestatic DILI respectively.

Limitations of our study include inherent selection bias, arbitrary laboratory eligibility criteria and lack of established standards for diagnosing DILI. The biochemical criteria we used in this study are largely consistent with recent case definitions proposed by an international panel of experts. DILI is a diagnosis of exclusion based on appropriate clinical history of medication exposure and thorough work up for competing etiologies. Each case was carefully and consistently adjudicated in a structured fashion by experienced hepatologists (10). Since our study is not population based, one needs to exercise cautious in interpreting the reported temporal trends of HDS DILI. Higher representation of HDS during later years of our study may simply be a function of higher capture rather than higher incidence of HDS DILI.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements / Grant Support

The DILIN (http://https://dilin.dcri.duke.edu/) is supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH)) as a Cooperative Agreement (U01s) under Grants: U01-DK065176 (Duke), U01-DK065201 (UNC), U01-DK065184 (Michigan), U01-DK065211 (Indiana), U01DK065193 (UConn), U01-DK065238 (UCSF/CPMC), U01-DK083023 (UTSW), U01-DK083027 (TJH/UPenn), U01-DK082992 (Mayo), U01-DK083020 (USC). Additional funding is provided by CTSA Grants: UL1 RR025761 (Indiana), UL1 RR025747 (UNC), UL1 RR024134 (UPenn), UL1 RR024986 (Michigan), UL1 RR024982 (UTSW), UL1 RR024150 (Mayo) and by the Intramural Research Program of the National Cancer Institute, National Institutes of Health (NIH). A complete list of participants in DILIN is given in the appendix.

Disclosures

Dr. Chalasani: Serves as a paid consultant to Abbvie, Salix, Aegerion, Lilly, Mitsubishi Tanabe, Wellpoint, and Boehringer-Ingelheim in the past 12 months. Received grant support from Intercept, Cumberland, Gilead, and Galectin.

Dr. Bonkovsky has served as a consultant to Alnylam, Clinuvel, Lundbeck, and Recordati in the past 12 months. He has research support from Clinuvel and Vertex.

Dr. Fontana: Received grant support from Gilead and Vertex and served as a paid consultant to Tibotec, Merck and GSK.

Drs. Serrano, Barnhart, Gu, Stolz and Talwalkar: No potential conflicts to declare;

Dr. Watkins: Served as a paid consultant to Abbvie, Actelion, Amgen, BMS, Boerringer–Ingelheim, Biogen-Idec, BMS, Diaichi-Sankyo, Genzyme, Gilead, GSK, Hoffman-LaRoche, Merck, Janssen, Novartis, Otsuka, Pfizer, Sanolfi- Aventis, and Takeda, in the past 12 months.

Dr. Lee: Served as a consultant to Lilly, Pfizer and Novartis. He received research support from BMS, GSK, Vertex and Merck.

Dr. Reddy: Served as a consultant to BMS, Gilead, Abbvie, Merck, Genentech-Roche, Vertex, and Janssen. He has research support from BMS, Abbvie, Gilead, Merck, Genentech-Roche, Vertex, Janssen, and Gen-Fit.

Dr. Navarro: Serves on the DSMB for GlaxoSmithKline.

Abbreviations

Alk P	Alkaline phosphatase
ALT	Alanine aminotransferase
ANA	Anti-nuclear antibody
AST	Aspartate aminotransferase
Chol	Cholestatic
DILI	Drug-Induced liver injury
DILIN	Drug-Induced Liver Injury Network
HC	Hepatocellular
HDS	Herbal and dietary supplement
IQR	Interquartile range
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
SJS	Stevens-Johnson syndrome
TEN	Toxic epidermal necrolysis

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List of DILIN Investigators, Coordinators, and Staff

Investigators

Jawad Ahmad, Icahn School of Medicine at Mount Sinai; Nancy Bach, Icahn School of Medicine at Mount Sinai; Meena Bansal, Icahn School of Medicine at Mount Sinai; Huiman X. Barnhart, Duke Clinical Research Institute; Kimberly Beavers, University of North Carolina-Chapel Hill; Herbert Bonkovsky, Wake Forest Baptist Medical Center; Francisco O. Calvo, National Institute of Diabetes and Digestive and Kidney Diseases; Naga Chalasani, Indiana University-Purdue; Charissa Chang, Icahn School of Medicine at Mount Sinai; Hari Conjeevaram, University of Michigan-Ann Arbor; Gregory Conner, University of North Carolina School of Medicine-Charlotte (Carolinas Medical Center); Jama Darling, University of North Carolina-Chapel Hill; Ynto de Boer, National Institute of Diabetes and Digestive and Kidney Diseases; Douglas Dieterich, Icahn School of Medicine at Mount Sinai; Frank DiPaola, University of Michigan-Ann Arbor; Francisco A. Durazo, University of California-Los Angeles (Pfleger Liver Institute); James E. (Jay) Everhart, National Institute of Diabetes and Digestive and Kidney Diseases; Robert J. Fontana, University of Michigan-Ann Arbor; Marwan S. Ghabril, Indiana University-Purdue; David Goldstein,

Duke Clinical Research Institute; Vani Gopalreddy, University of North Carolina School of Medicine-Charlotte (Carolinas Medical Center); Priya Grewal, Icahn School of Medicine at Mount Sinai; Paul H. Hayashi, University of North Carolina-Chapel Hill; Jay Hoofnagle, National Institute of Diabetes and Digestive and Kidney Diseases; Neil Kaplowitz, University of Southern California; Suthat Liangpunsakul, Indiana University-Purdue; Steven Lichtman, University of North Carolina-Chapel Hill; Lawrence Liu, Icahn School of Medicine at Mount Sinai; Victor J. Navarro, Albert Einstein Medical Center; Joseph Odin, Icahn School of Medicine at Mount Sinai; Simona Rossi, Albert Einstein Medical Center; Mark Russo, University of North Carolina School of Medicine-Charlotte (Carolinas Medical Center); Thomas Schiano, Icahn School of Medicine at Mount Sinai; José Serrano, National Institute of Diabetes and Digestive and Kidney Diseases; Averell H. Sherker, National Institute of Diabetes and Digestive and Kidney Diseases; Andrew Stolz, University of Southern California; Raj Vuppalanchi, Indiana University-Purdue; Paul Watkins, University of North Carolina-Chapel Hill; Steven Zacks, University of North Carolina-Chapel Hill;

Coordinators/Site Management

Amanda Balasco, University of North Carolina School of Medicine-Charlotte (Carolinas Medical Center); Kristin Chesney, University of Michigan-Ann Arbor; Audrey Corne, Indiana University-Purdue; Sherrie Cummings, Indiana University-Purdue; Gale Groseclose, University of North Carolina School of Medicine-Charlotte (Carolinas Medical Center); Alex Hammett, Duke Clinical Research Institute; Judy Hooker, Wake Forest Baptist Medical Center; Varun Kesar, Icahn School of Medicine at Mount Sinai; Sophana Mao, University of Michigan-Ann Arbor; Kenari Marks, Duke Clinical Research Institute; Regina McFadden, University of North Carolina School of Medicine-Charlotte (Carolinas Medical Center); Yolanda Melgoza, University of California-Los Angeles (Pfleger Liver Institute); Sherif Mikhail, Icahn School of Medicine at Mount Sinai; Susan Milstein, University of Southern California; Wendy Morlan, Indiana University-Purdue; Val Peacock, University of California-Los Angeles (Pfleger Liver Institute); Nidia Rosado, Duke Clinical Research Institute; Tracy Russell, University of North Carolina-Chapel Hill; Maricruz Vega, Albert Einstein Medical Center; Manisha Verma, Albert Einstein Medical Center; Patricia Walker, University of Michigan-Ann Arbor; Rachana Yalamanchili, Icahn School of Medicine at Mount Sinai;

Additional Staff

Michelle McClanahan-Crowder, Duke Clinical Research Institute; Katherine Galan, Duke Clinical Research Institute; Jiezhun (Sherry) Gu, Duke Clinical Research Institute; Tuan Chau, Duke Clinical Research Institute; Kowsalya Ragavan, Duke Clinical Research Institute; Hoss Rostami, Duke Clinical Research Institute; Carmel Puglisi-Scharenbroich, Duke Clinical Research Institute; Rebecca J. Torrance, National Institute of Diabetes and Digestive and Kidney Diseases; Rebekah Van Raaphorst, National Institute of Diabetes and Digestive and Kidney Diseases;

Table 1

Demographic and Selected Clinical Features for the 899 Subjects Studied. Comparisons by Patterns of Drug-Induced Liver Injury.

	Entire cohort (N=899) 100%	**HC* (n=484) 53.8%**	**Chol* (n=210) 23.4%**	**Mixed (n=205) 22.8%**	**P value†**
Age (years, mean [SD])	49 [17]	45 [17]	54 [16]	50 [17]	< 0.001
Females (%)	59	65	51	52	<0.001
Self-reported race (%)					
White	79	74	84	84	0.003
Black or African-American	12	13.5	11	8	
Other/Multiracial	10	12	5	8	
BMI (kg/m^2, mean [SD])	27 [6.5]	28 [6..8]	27 [6.3]	27 [6.1]	0.2
Prior drug allergies (%)	44	44	47	42	0.6
Immuno-allergic features (%)	15	12	17	21	0.018
Preexisting Liver Disease (%)	9.9	9.9	13.3	6.3	0.059
Diabetes mellitus (%)	25	23	33	20	0.004
Latency (days in median, IQR)	36 [19–88]	46 [22–104]	31 [16–72]	31 [18–51]	<0.001
Jaundice (%)	70	65	78	75	<0.01
Liver Biochemistries –DILI recognition					
ALT (U/L, mean [SD])	825 [1105]	1275 [1329]	202 [160]	379 [226]	<0.001
AP (U/L, mean [SD])	288 [254]	187 [110]	497 [371]	306 [206]	<0.001
Total bilirubin (mg/dl, mean [SD])	6.7 [6.6]	6.3 [6.6]	7.8 [7.3]	6.4 [6.0]	0.005
INR	1.4 [1.0]	1.6 [1.2]	1.2 [0.5]	1.3 [0.6]	<0.001
Liver Biochemistries – Peak values					
ALT (U/L, mean [SD])	1008 [1221]	1510 [1431]	339 [445]	506 [439]	<0.001
AP (U/L, mean [SD])	406 [388]	271 [252]	682 [532]	440 [317]	<0.001

	Entire cohort (N=899) 100%	HC* (n=484) 53.8%	Chol* (n=210) 23.4%	Mixed (n=205) 22.8%	P value†
Total bilirubin (mg/dl, mean [SD])	13 [12]	12 [11.3]	15 12.5]	13.3 [12.1]	<0.001
INR	1.7 [1.5]	1.8 [1.8]	1.6 [1.15]	1.5 [1.1]	0.007
Peripheral eosinophilia (>500/μL) (%)	11	7.2	14.6	15.8	<0.001
Improvement in liver tests – median days					
Peak ALT to below ULN	71	79	113	59	0.01
Peak AP to below ULN	96	48	183	90	<0.001
Peak bilirubin to ≤ 1 mg/dL	70	66	77.5	74	0.3
Causality Assessment (%)					
Definite/ Highly likely/ Prob, n	235 / 466 / 198	120 /255 / 109	47/109/54	68/102/35	
%	26 / 52 / 22	25 / 53 / 22	22 / 52 / 26	33 / 50 / 17	0.056
Severity of Liver Injury (%)					
Mild	24	29	15	20	<0.001
Moderate	21	15	27	29	
Moderate-hospitalized	29	26	33	34	
Severe	19	21	21	13	
Fatal	7	9	4	4	
Death, at any time point (%)	6.2	5.4	9	5.4	0.17
- Percent Liver –related (%)	49	58	56	18	0.079
Liver Transplantation (%)	4	6.2	2.9	0	<0.001
Chronic DILI (%)	17	13	31	14	<0.001

Abbreviations: ALT, serum alanine aminotransferase; AP, serum alkaline phosphatase; BMI, body mass index; Chol, cholestatic; DILI, drug-induced liver injury; HC, hepatocellular; INR, international normalized ratio; IQR, interquartile range (25–75%); ULN, upper limit of normal

†P-values compare HC, Chol, and mixed categories.

Table 2

Top ten therapeutic classes and individual agents to cause DILI in the DILIN Prospective Study

	Therapeutic classes	n		Individual agents¶	n
1	Antimicrobials	408	**1**	Amoxicillin-Clavulanate	91
2	Herbal and dietary supplements	145	**2**	Isoniazid	48
3	Cardiovascular agents	88	**3**	Nitrofurantoin	42
4	Central nervous system agents	82	**4**	Sulfamethoxazole/Trimethoprim	31
5	Anti-neoplastic agents	49	**5**	Minocycline	28
6	Analgesics	33	**6**	Cefazolin	20
7	Immunomodulatory	27	**7**	Azithromycin	18
8	Endocrine	20	**8**	Ciprofloxacin	16
9	Rheumatologic	13	**9**	Levofloxacin	13
10	Gastrointestinal	12	**10**	Diclofenac	12

¶Herbal and dietary supplements are not included. Also, in cases of multiple implicated agents, the primary implicated agent was considered for this analysis.

Table 3

Comparison of selected characteristics of DILI due to top 5 classes of prescription agents

	Antimicrobials (n=408)	Cardiovascular (n=88)	CNS agents (n=82)	Antineoplastics (n=49)	Analgesics (n=33)
Age (years, mean ± SD)	50± 17	55 ±15	38± 18	52± 14	53± 15
Females (%)	58	65	63	69	82
Latency (days in median , IQR)	31 (16–61.5)	86 (45–186)	35 (22–63)	87.5 (36–291)	47(23–111)
Pattern of liver injury HC/Chol/Mixed (%)	48/26/26	53/28/18	68/12/20	51/35/14	73/9/18
Liver Biochemistries -DILI recognition					
ALT (U/L, mean± SD)	728± 1072	850± 787	1085± 1401	511± 541	923± 671
AP (U/L, mean± SD)	307± 242	411 ± 428	256± 178	183± 104	257± 174
Total bilirubin (mg/dL, mean± SD)	5.9± 5.6	5.8± 6.3	4.8±5.8	5.9±6.1	7.3±8.3
Liver Biochemistries - Peak values					
ALT (U/L, mean± SD)	893± 1182	1063± 975	1412± 1634	717± 666	1035± 668
AP (U/L, mean± SD)	416± 373	527± 579	368± 302	388± 502	361 ± 285
Total bilirubin (mg/dL, mean± SD)	11.5±10.7	11.4± 11	9.7± 10.5	10.5± 10.1	12± 12.6
Hy's law (%)	25	23	30	20	29
Peripheral eosinophilia (>500/μL) (%)	14	9	17	7	30
ANA >1:80 (%)	22.5	26	20	16	18
Improvement in liver tests – Median days					
- Peak ALT to below ULN	72	64	49	106	97
- Peal AP to below ULN	83	108	43	223	160
- Peak bilirubin to ≤ 1 mg/dL	73	93	65	63	99
Causality Assessment Definite/ Very likely/ Probable [%]					
Severity of Liver Injury (%)					

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	Antimicrobials (n=408)	Cardiovascular (n=88)	CNS agents (n=82)	Antineoplastics (n=49)	Analgesics (n=33)
Mild	23	30	28	33	36
Moderate	26	21	10	16	21
Moderate-hospitalized	29	26	26	18	15
Severe	14	18	30	22	24
Fatal	6.9	5.7	6	10	3
Death, at any time (% of n in column)	5.1	5.7	6.1	29	3
- Percent Liver–related	62	50	20	29	0
Liver Transplantation (% of n in column)	3.9	2.3	3.7	0	0
Chronic DILI (%)	15	17.7	7.5	48.7	16.1

Abbreviations: ALT, serum alanine aminotransferase; ANA, anti-nuclear antibody; AP, serum alkaline phosphatase; BMI, body mass index; Chol, Cholestatic; CNS, central nervous system; DILI, drug-induced liver injury; HC, hepatocellular; INR, international normalized ratio; IQR, interquartile range (25–75%); SD, standard deviation; ULN, upper limit of normal

Table 4

Selected characteristics among the elderly (≥65yo), compared to younger subjects (≤65yo)

	≥ 65 years (n=149)	< 65 years (n=750)	P value
Age (years, mean [SD])	73 [6]	44 [14]	
Females (%)	60	59	0.8
Self-reported race (%)			0.12
White	85	77	
Black or African-American	7	13	
Other/Multiracial	8	10	
BMI (kg/m^2, mean [SD])	27 [5]	28 [6.8]	0.4
Prior drug allergies (%)	54	42	0.015
Preexisting Liver Disease (%)	10.1	9.9	0.9
Concomitant medicines (%)			
0–2 / 3–5 / >5	16/26/58	26/26/48	0.03
Diabetes mellitus (%)	30	24	0.1
Top 5 implicated classes of agents (%)	Antimicrobials (57.7%) Cardiovascular (14.8%) HDS (8.1%) Antineoplastic (4%) Analgesics (3.4%)	Antimicrobials (43%) HDS (17.7%) CNS agents (10.4%) Cardiovascular (8.8%) Antineoplastic (5.7%)	<0.001
Latency (days in median , IQR)	35 [18–99]	36 [19–84]	0.8
Jaundice (%)	67	71	0.4
Pattern of liver injury			
HC/Chol/Mixed (%)	39/36/25	57/21/22	<0.001
Liver Biochemistries –DILI recognition			
ALT (U/L, mean [SD])	619.5 [860.5]	866± [1143.5]	0.007
AP (U/L, mean [SD])	410 [361]	264 [220]	<0.001
Total bilirubin (mg/dl, mean [SD])	7.0 [6.7]	6.6 [6.6]	0.4
INR	1.6 [1.2]	1.4 [0.9]	0.9
Hy's law (%)	18	32	0.001
Liver Biochemistries – Peak values			
ALT (U/L, mean [SD])	757 [911]	1057 [1268]	0.002
AP (U/L, mean [SD])	520 [446]	383 [372]	<0.001
Total bilirubin (mg/dl, mean [SD])	14 [12]	13 [12]	0.4

	≥ 65 years (n=149)	< 65 years (n=750)	P value
INR	1.8 [1.65]	1.7 [1.5]	0.9
Peripheral eosinophilia (>500/μL) (%)	11	11	1.0
Improvement in biochemistries – days in median			
- Peak ALT to below ULN	62	74	0.5
- Peal AP to below ULN	106	90	0.5
- Peak bilirubin to ≤ 1 mg/dL	78	68	0.8
Causality Assessment (%)			
Definite/ Highly likely/ Probable	25.5/55/19.5	26/51/23	0.6
Severity of Liver Injury (%)			
Mild	31	22	0.08
Moderate	19.5	22	
Moderate-hospitalized	29	29.5	
Severe	13	20	
Fatal	8	6.7	
Death, at any time point (%)	8.7	5.7	0.2
- Proportion of Liver –related (%)	54	48	0.8
Liver Transplantation (%)	2	4.4	0.25
Chronic DILI (%)	11.4	18.7	0.04

Abbreviations used: ALT, serum alanine aminotransferase; AP, serum alkaline phosphatase; BMI, body mass index; Chol, cholestatic; DILI, drug-induced liver injury; HC, hepatocellular; INR, international normalized ratio; IQR, interquartile range (25–75%); SD, standard deviation; ULN, upper limit of normal

Table 5

Characteristics of Nine Subjects with DILI who Exhibited Features of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

	Causative Agent	Age/Sex/ Ethnicity	Latency (days)	Pattern	Eosinophilia	Peak Serum			Causality score	Severity score	Steroids given	Outcome
						ALT [U/L]	AP [U/L]	TBR [mg/dL]				
1	Lamotrigine	12/F/AA	34	HC	No	862	846	11.5	Definite	3	Yes	Recovery
2	Moxifloxacin	44/M/Asian	9	HC	No	1311	379	3.6	Definite	3	Yes	Recovery
3*	Diclofenac	60/F/Asian	46	HC	No	1895	303	38	Highly likely	Fatal	Yes	Fatal (nonhepatic, liver tests improved)
4	Azithromycin	11/F/W	64	HC	No	418	1112	13	Probable	4	Yes	Chronic DILI. Developed Bronchiolitis with bronchiectasis. Died from pulmonary complications
5*	Cefalexin/lamotrigine	48/F/H	14	HC	No	1808	2414	59	Highly likely¶	Fatal	Yes	Fatal
6*	Azithromycin	20/F/AA	2	HC	No	1351	718	20	Highly likely	4	Yes	Chronic DILI
7	Lamotrigine	21/M/W	13	HC	No	1272	119	0.7	Definite	3	Yes	Recovery
8	Carbamazepine*	43/F/W	30	Mixed	No	812	1005	23.5	Highly likely	Fatal	Yes	Fatal (non-hepatic). Liver tests normalized
9	Nitrofurantoin	35/F/AA	7	Mixed	No	855	678	19.8	Probable	4	Yes	Alive at last follow-up

Abbreviations: AA, African-American; ALT, serum alanine aminotransferase; AP, serum alkaline phosphatase; DILI, drug-induced liver injury; F, female; HC, hepatocellular; M, male; TBR, total bilirubin; W, white; H, Hispanic;

*these subjects experienced TEN.

¶104–54 overall causality score was highly likely with cephalexin scored as probable and lamotrigine as possible cause.

Table 6

DILI in Subjects with and without Known Pre-existent Liver Disease

	Known pre-existent liver disease (n=89)	No known pre existent liver disease (n=810)	P value
Age (years, mean ± SD)	52± 12.4	48 ±17.4	0.08
Females (%)	54	59	0.4
Self-reported race (%)			0.35
White	73	79	
Black or African-American	13.5	11.5	
Other/Multiracial	13.5	9	
BMI (kg/m^2, mean ± SD)	28± 6.9	27 ± 6.5	0.72
Prior drug allergies (%)	46	44	0.7
Diabetes mellitus (%)	38	23	0.004
Top 5 implicated classes of agents (%)	Antimicrobials (51%) HDS (13.5%) Cardiovascular (6.7%) Antineoplastic (6%) CNS agents (4.5%)	Antimicrobials (45%) HDS (16%) Cardiovascular (10.1%) CNS agents (9.6%) Antineoplastic (5.4%)	0.2
Latency (days in median , IQR)	34 (20–63)	36 (19–89)	0.3
Jaundice (%)	70	70	0.9
Pattern of liver injury			
HC/Chol/Mixed (%)	54/31/15	54/22/24	0.058
Liver Biochemistries –DILI recognition			
ALT (U/L, mean± SD)	689± 1037	840± 1112	0.12
AP (U/L, mean± SD)	284± 310	289± 248	0.11
Total bilirubin (mg/dl, mean± SD)	7.4± 7.0	6.6± 6.6	0.3
INR	1.6± 0.9	1.4± 1.0	0.2
Hy's law (%)	31	29	0.8
Liver Biochemistries – Peak values			
ALT (U/L, mean± SD)	821 ± 1086	1028± 1234	0.08
AP (U/L, mean± SD)	380± 458	408± 380	0.02
Total bilirubin (mg/dL, mean± SD)	13± 11.4	13± 12	0.8
INR	1.8± 1.6	1.7± 1. 5	0.12
Peripheral eosinophilia (>500/μL) (%)	12	11	0.7

	Known pre-existent liver disease (n=89)	No known pre existent liver disease (n=810)	P value
Improvement in biochemistries – days in medianPeak ALT to below ULN			
- Peal AP to below ULN	64	73	0.3
- Peak bilirubin to ≤ 1 mg/dL	139	93	0.5
	64	70	0.5
Causality Assessment (%)			
Definite/ Highly likely/ Probable	17/49/34	27/52/21	0.009
Severity of Liver Injury (% of column total)			
Mild	29	23	0.09
Moderate	15	22	
Moderate-hospitalized	27	30	
Severe	17	19	
Fatal	12.4	6.3	
Death, at any time point (%)	16	5.2	<0.001
- Percent Liver –related	57	46	0.5
Liver Transplantation (%)	3.4	4.1	1.0
Chronic DILI (%)	13.7	17.9	0.4

Abbreviations: ALT, serum alanine aminotransferase; AP, serum alkaline phosphatase; BMI, body mass index; Chol, Cholestatic; DILI, drug-induced liver injury; HC, hepatocellular; INR, international normalized ratio; IQR, interquartile range (25–75%); SD, standard deviation; ULN, upper limit of normal

Table 7

Comparison of Subjects with Short vs. Long Latency DILI

	Short latency (≤ 7 days) (n=41)	Long latency (>365 days) (n=60)	P value
Age (years, mean ± SD)	49± 17	50±22	0.5
Females (%)	56	70	0.2
Self-reported race (%)			0.2
White	82.5	93	
Black or African-American	7.5	3	
Other/Multiracial	10	3	
BMI (kg/m^2, mean ± SD)	27± 6.9	27.3 ± 6.7	0.9
Prior drug allergies (%)	46	55	0.4
Diabetes mellitus (%)	24	28	0.8
Preexisting liver disease (%)	14.6	3.3	0.06
Top 5 implicated classes of agents	Antimicrobials (71%) HDS (7%)* Analgesics (5%) Immunomodulatory (5%) CNS or cardiovascular or Endocrine or GI or hematological agents (2%)	Antimicrobials (45%) Antineoplastic (15%) Cardiovascular (13%) CNS agents (12%) Immunomodulatory (6.7%)	0.03
Latency (days in median , IQR)	5 (3–7)	643 (483–1297)	<0.001
Jaundice (%)	58.5	53	0.7
Hypersensitivity features (%)			
• Fever	27	13	0.1
• Itching	29	40	0.3
• Rash	22	20	0.8
• SJS	0	0	
Pattern of liver injury			
HC/Chol/Mixed (%)	49/22/29	57/30/13	0.14
Liver Tests –at DILI recognition			
ALT (U/L, mean± SD)	831 ± 1500	712± 725	0.9
AP (U/L, mean± SD)	244± 145.6	290± 251	0.8
Total bilirubin (mg/dL, mean± SD)	4.1±4.3	6.1± 7.4	0.6
INR	1.5± 0.9	1.5± 0.8	0.3
Hy's law (%)	17.5	17	1.0

	Short latency (≤ 7 days) (n=41)	Long latency (>365 days) (n=60)	P value
Liver Tests – Peak values			
ALT (U/L, mean± SD)	1008± 1648	863± 791344±338	0.6
AP (U/L, mean± SD)	335± 234.5	8.9±9.3	0.6
Total bilirubin (mg/dL, mean± SD)	8± 9.2	1.8± 1.9	0.8
INR	1.8± 1.7		0.5
Peripheral eosinophilia (>500/μL) (%)	7.7	8.6	1.0
Improvement in liver tests –median d			
- Peak ALT to below ULN	68	98	0.07
- Peal AP to below ULN	84	129	0.99
- Peak total bilirubin to ≤ 1 mg/dL	36	76	0.3
mg/dL			
Causality Assessment			
Definite/ Highly likely/ Probable	10/54/37	15/62/23	0.3
Severity of Liver Injury (%)			
Mild	32	37	0.17
Moderate	27	15	
Moderate-hospitalized	22	12	
Severe	12	28	
Fatal	7.3	8.3	
Death, at any time point (%)	4.9	13.3	0.2
-Percent Liver –related	50	71	1.0
Liver Transplantation (%)	2.4	3.3	1.0
Chronic DILI (%)	12.5	31	0.07
Causative agents	Moxifloxacin (4) Azithromycin (3) Ciprofloxacin (3) HDS (3) Rifampicin (2) Levofloxacin (2) Nitrofurantoin (1), Azathioprine (1), Amoxicillin (1), Amox-clavulanate (1), Antithymocyte globulin (1), Cefaclor (1), Cefazolin (1), Cefotaxime (1), Ceftriaxone (1), Dalteparin (1), Diclofenac (1), Erythromycin (1), Fluconazole (1), Meropenam (1), Methylprednisolone (1), Micafungin (1), Nicotinic acid (1), Oxaprozin (1), Phenytoin (1), Piperacillin-tazobactam (1), Ranitidine (1), TMP-SMX (1), Telithromycin (1),	Nitrofurantoin (16) Minocycline (10) Amiodarone (3) Mercaptopurine (3) Atomoxetine (2) Atorvastatin (2) Rosuvastatin (2) Tamoxifen (2) Oxaliplatin (2) Buproprion (2), Nicotinic acid (1), Azathioprine (1), Diclofenac (1), Etravirine (1), Imatinib (1), Interferon-beta(2), Fluoxetine (1), Metformin (1), Methotrexate (1), Methylphenidate (1), Promethazine (1), Tacrolimus(1), Testosterone (1), Topiramate (1), HDS (1)	

	Short latency (≤ 7 days) (n=41)	Long latency (>365 days) (n=60)	P value
	Vancomycin (1)		

Abbreviations: ALT, serum alanine aminotransferase; AP, serum alkaline phosphatase; BMI, body mass index; Chol, Cholestatic; DILI, drug-induced liver injury; HC, hepatocellular; INR, international normalized ratio; IQR, interquartile range; SD, standard deviation; AMX, sulfamethoxazole; TMP, trimethoprim; ULN, upper limit of normal.

* Implicated HDS agents in 3 cases with short latency were (a) multiple CAM products - Extenze, AMP muscle building formula; (2) Multiple CAM products – Bulgarian mushrooms, Aloe Vera, Boldo tea; and (3) Meganite