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Frequency, Clinical Presentation, and Outcomes of Drug-Induced Liver Injury after Liver Transplantation

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Abstract

Background—Drug-induced liver injury (DILI) is increasingly recognized as a common cause of acute hepatitis. The clinical impact of DILI following liver transplantation (LT) is not known.

Aims—To describe the frequency, clinical presentation, and outcomes of DILI among LT recipients.

Methods—LT recipients with possible DILI were identified using electronic pathology and clinical note database retrieval tools. Diagnostic criteria were applied to identify cases of DILI.

Results—Among 1689 LT recipients, 29 individuals with DILI (1.7%) were identified. Mean age was 52 years with 52 % women. Major indications for LT were primary sclerosing cholangitis (28%), cholangiocarcinoma (14%), and hepatocellular carcinoma (14%). Severity of DILI was mild or moderate in 92% of cases. Nausea or diarrhea (31%), jaundice (24%), and pruritus (10%) were the most common symptoms at diagnosis. Mean ALT was 204±263 U/L, AST 108 ± 237 U/L, ALP 469 ± 689 U/L, and TB 1.9±10.3 mg/dL. Median duration of medication use until DILI diagnosis was 57 days, and major classes of agents were antibiotics (48%), immunosuppressive agents (14%), and antihyperlipidemic drugs (7%), Trimethoprim-sulfamethoxazole was the most common single implicated agent (n=11). Serum liver enzymes improved within a median time of 34 days (range, 5-246 days) after drug withdrawal. Hepatic re-transplantation or death did not occur. Among 50 cases with possible DILI explained by other causes, 13 (26%) individuals had no alternate diagnosis despite histology compatible with DILI.

Conclusions—DILI is a rare yet under-recognized event among LT recipients. The majority of cases are not clinically severe, and resolve following drug cessation without hepatic retransplantation or death.

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Introduction

Drug-Induced liver injury (DILI) is a severe health condition that may result in the need for liver transplantation or death in up to 10% of cases with hepatocellular jaundice (1). There are two different types of DILI. The first is a dose-dependent DILI which is typical for acetaminophen overdose, while idiosyncratic DILI is a dose – independent phenomenon associated with a number of medications and herbal/dietary supplements (1,2). The diagnosis of idiosyncratic DILI requires exclusion of known etiologies for acute and chronic liver injury, in addition identifying a temporal association between drug ingestion and presentation of liver injury (3). Removal of the offending agent with improvement in liver injury ("dechallenge") further strengthens the diagnosis of DILI when this is observed (1-4).

A number of prospective studies have recently described the clinical epidemiology of DILI in persons with native liver injury (2,5,6). Traditionally, the diagnosis of DILI has been more difficult to make among patients with a history of liver transplantation (LT) given the presence of complications such as reperfusion injury, acute viral hepatitis, or acute cellular rejection (7). However, it is important to list DILI in the differential diagnosis for patients with allograft dysfunction as potentially hepatotoxic medications are prescribed for prophylaxis against opportunistic infections (8). In addition, LT recipients have an increased frequency of *de novo* and recurrent non-alcoholic fatty liver disease which can present with elevated serum liver enzymes. Recently, a checklist of minimal elements considered essential for the diagnosis and causality assessment of DILI has been proposed (9). In turn, we sought to apply these criteria to identify the prevalence, clinical features, and outcomes of DILI in our population of LT recipients.

Materials and Methods

Patient Population

The source population for our study cohort included consecutive patients who underwent at least 1 liver transplant procedure between March 1, 1985 and June 30, 2010 at the Mayo Clinic in Rochester, MN. The study protocol was approved by the Institutional Review Board of the Mayo Clinic and was carried out in accordance with institutional guidelines. All participating patients gave informed consent.

Liver Transplantation Protocol

Between 1993 and 1997, liver transplantation was performed with excision of the retrohepatic vena cava followed by donor caval interposition using portovenous and venovenous bypass. After 1997, caval-sparing hepatectomy became the standard technique in our center and is performed in most cases. Since 2000, we have also performed living donor liver transplants using standard approaches. Biliary reconstruction is generally with a choledochocholedochostomy, but patients with primary sclerosing cholangitis (PSC) or cholangiocarcinoma (CCA) undergo Roux en Y choledochojejunostomy (10).

The protocol used for immunosuppressive therapy after LT included cyclosporine A as the primary agent between 1985 and 1986. Tapering doses of prednisone were also included. After 1986, the primary immunosuppression regimen was changed to cyclosporine A, azathioprine, and prednisone. Beginning in 1993, tacrolimus was introduced into the immunosuppression protocol in combination with azathioprine and prednisone. Over time, tacrolimus became the preferred calcineurin inhibitor in all patients undergoing LT. In 1999, mycophenolate mofetil was used in place of azathioprine for all patients. Oral prednisone was tapered to discontinuation between 4 and 6 months from the year 1999 onwards. Within the first year after LT, a clinical algorithm was employed that allowed for the discontinuation of mycophenolate mofetil. If an individual patient experienced no episodes

of acute cellular rejection within 2 months after LT, mycophenolate mofetil could be discontinued. If 1 episode of acute cellular rejection occurred within the first 2 months, an additional 2 months of mycophenolate mofetil was required. If 2 episodes of acute cellular rejection or at least 1 episode of steroid resistant rejection occurred within the first 2 months, patients were required to continue mycophenolate mofetil for a duration of 1 year before considering tapering to discontinuation.

Protocol liver biopsies were performed at day 7, 4 months, 1 year, and then annually from 1985 until 2004. Thereafter, only patients transplanted for chronic hepatitis C underwent protocol liver biopsies according to this schedule. All patients were referred for liver biopsy whenever evidence for hepatic parenchymal injury was observed by either active monitoring of serum liver enzymes (ranging from weekly to every 3 months depending on the number of years since LT) or clinical evaluation of symptoms (11).

Identification of DILI in Liver Transplant Recipients

Patients with evidence for DILI after LT were identified within the source population using two specific approaches. Given the likelihood that liver histology would be obtained in LT recipients with suspected DILI to exclude other causes of allograft dysfunction, a computerized search of an institutional database maintained by the Division of Anatomic Pathology for all liver biopsy reports since 1985 was performed. Text reports of all tissue specimens obtained for clinical purposes are housed in this database. The search terms used for this investigation included: “adverse drug reaction” and drug-induced liver injury”. The identification of these terms in any location within the pathology report identified a potential case of DILI for this study. Utilizing this strategy, we identified a total of 80 patients with possible DILI. Four of these patients were transplanted because of DILI and were excluded, leaving a total of 76 subjects.

In addition, a computerized data retrieval tool was used to search clinical notes within the Institution’s electronic health record for cases of possible DILI. This was performed to assist in verifying potential DILI cases and to determine if some patients were given a diagnosis of DILI without performance of a liver biopsy. Using this tool, we utilized the search terms “adverse drug reaction AND liver AND transplant” as well as “drug AND hepatotoxicity AND liver transplantation”. The time period examined was between January 1, 1995 and June 30, 2010. Using these search terms, a total of 869 individual patients were retrieved. Manual review of electronic clinical notes for these patients revealed a total of 3 unique cases that were not identified from the electronic pathology database. None of these patients had undergone liver biopsy according to clinical records. Thus, a total of 79 patients were identified as having pot ential DILI.

Data Collection

Clinical information for this study was abstracted from the electronic health record and Mayo Clinic Liver Transplantation Database. Specific variables included age; sex; primary disease; date of transplantation; recipient human leukocyte antigen (HLA) typing; date of DILI onset and diagnosis; donor age, sex and HLA typing; liver biopsy results; laboratory results including ALT, AST, alkaline phosphatase (ALP), total bilirubin (TB), INR, and eosinophil count; date of first abnormal results and date of normal results after resolution of DILI episode; serologies including IgM anti-HAV, IgM anti-HBc, HBs antigen, anti-HCV antibody, HCV RNA, EBV IgM Ab, CMV IgM, ANA level; and imaging results from ultrasound, computed tomography, magnetic resonance imaging, and/or endoscopic or percutaneous cholangiography. The presence or absence of systemic hypotension, alcohol use, and sepsis were also noted. Clinical features including fever, pruritus, jaundice, rash, and gastrointestinal symptoms (nausea/vomiting/abdominal pain) were recorded. Finally, the

type of immunosuppressive agent, dose, and duration of use at the time of the possible DILI episode was recorded. Liver histology was re-read by a single hepatopathologist (S.O.S.) who was blinded to clinical information pertaining to each case. Salient features on histology were identified and recorded. These variables were collected in accordance with recommendations for securing minimum important elements that are needed to make an accurate diagnosis of DILI (Table 1). (9)

The offending agent (s) temporally associated with possible DILI, including dose and duration of use, were also recorded. In the clinical characterization of DILI, the ratio of serum ALT (as a multiple of its ULN) to serum alkaline phosphatase (as a multiple of its ULN) has been designated as the R (for ratio) value. Hepatocellular DILI is defined as $R \geq 5$, cholestatic as $R \leq 2$, and "mixed" as $R > 2$ to $R < 5$.

Diagnosis of DILI

A definite diagnosis of DILI was based on the presence of fulfilling all of the required elements representing strict diagnostic criteria for DILI (with the exception of drug rechallenge) in addition to liver histology compatible with DILI. Major elements from the diagnostic criteria that were required for a diagnosis of DILI included the potential drug and its dose, dates of start and discontinuation of therapy (or time from onset of event), the date of onset and/or time of first abnormal laboratory test result, initial laboratory results at presentation (including serum liver enzymes and total bilirubin), and liver histology results. For some of the checklist items, specific tests were not repeated at the time of suspected DILI (i.e. repeat HCV RNA level in a patient transplanted for PSC) but were checked previously.. In turn, subjects with DILI could not have evidence for an alternate diagnosis such as acute cellular rejection, chronic ductopenic rejection, recurrent disease, biliary stricture, hepatic artery thrombosis, and portal/hepatic venous stenosis or thrombosis. For patients with all of the minimum elements required for DILI but no available liver histology, a diagnosis of possible DILI was made. The severity of each DILI episode was categorized as one of 5 levels (mild, moderate, moderate-hospitalized, severe, and fatal/transplant) as described elsewhere (12).

Statistical Analyses

The results are displayed in tables, with categorical variables presented as numbers and percentage and continuous variables presented as mean and standard deviation or median (range), when appropriate.

Results

Between March 1, 1985 and June 30, 2010, a total of 1689 patients underwent 2090 liver transplants including 19 familial amyloidosis domino donor transplants and 108 living donor transplants.. Following our search strategies, we identified 79 patients with a potential diagnosis of DILI. Using the checklist of minimum diagnostic elements for the diagnosis of DILI, only 28 individuals met criteria for definite DILI and 1 individual was considered to have possible DILI (i.e. all of the minimum elements but no liver histology). An additional 50 individuals with liver histology suggestive of DILI were excluded based on the identification of an alternate etiology as surmised by the treating physician (i.e. non-DILI group).

Demographic and Clinical Features of DILI Patients

Among the 29 individuals with evidence for DILI, the mean age was 52 years, and 52 % were women. Indications for LT were primary sclerosing cholangitis (PSC) (28%), cholangiocarcinoma (14%), hepatocellular carcinoma (14%), other indications (14%),

metabolic liver disease (10%), primary biliary cirrhosis (PBC) (7%), hepatitis C (3%), alcohol (3%), autoimmune hepatitis (3%), and hepatitis B (3%). The mean donor age was 36 years (range, 5 to 76 years) and 56% of grafts were donated by women.

The clinical severity of DILI was assessed as mild in 71%, moderate in 21%, moderate-severe in 4%, and severe in 4% of cases. One or more clinical features of DILI at initial presentation was reported in 48% of patients. The most common symptoms were gastrointestinal including nausea and/or diarrhea (31%), jaundice (24%), pruritus (10%), fever (10%), and rash (3%). At the time of DILI recognition, the median (SD) values of serum liver enzymes were ALT 204±263 U/L, AST 108 ± 237 U/L, ALP 469 ± 689 U/L, and TB 1.9±10.3 mg/dL. Serum AST and ALT levels ≥ 5 times baseline occurred in 41% and 37% of cases, respectively. Serum ALP levels ≥2 times above baseline were noted in 48% of cases, while serum TB levels ≥ 2.5 times above baseline were observed in 38% of cases. The R value was calculated in 27 patients who had both serum ALT and alkaline phosphatase values available on the day of DILI recognition. A total of 24 (89%) cases were classified as cholestatic, 2 (7.5%) were hepatocellular, and 1 (3.7%) was mixed. Notably, the R value was concordant with histological findings in only 37% of cases.

The distribution of timing for DILI after LT is described in Figure 1. A diagnosis of DILI occurred between days 1 to 30 after LT in 4 patients, day 31 to 90 in 8 patients, day 91 to 150 in 7 patients, day 151 to 300 in 0 patient, day 301 to 500 in 2 patients, and beyond day 501 in 8 patients. The median duration of use for agents implicated as causing DILI was 57 days prior to the onset of abnormal serum liver enzymes and/or symptoms (ranging from 15 to 965 days).

Liver histology was available in 28 of 29 cases where biopsy was performed. Histological features were primarily identified as cholestatic (9 cases) or necroinflammatory (12 cases). Mixed features of both necroinflammation and cholestasis were found in 3 patients. Three patients presented with features of lobular hepatitis with or without necrosis/apoptosis. One patient showed atypical findings of portal and periportal hepatitis with lymphocytic and neutrophilic cholangitis.

Causative Agents

Prescription medications were the cause of definite or possible DILI in all patients except one case where herbal tea was identified as the offending agent. In 8 patients (28%), more than one prescription medicine was suspected as a potential cause of DILI, yet for this study a single agent was identified to be the most likely culprit. A complete list of all implicated agents is found in Table 2. The major classes of agents were antibiotics (48%), immunosuppressive agents (14%), antihyperlipidemic drugs (7%), antivirals (7%), antifungals (3%), and others (21%). The most common implicated agent was trimethoprim – sulfamethoxazole (n = 11).

Clinical Outcome of DILI

Serum liver enzyme values including total bilirubin improved to baseline values over a median duration of 34 days (range, 5 to 246 days) after drug withdrawal in all cases. There were no cases associated with chronically elevated serum liver tests, and none of the cases resulted in the need for hepatic retransplantation or death.

Subjects with Liver Histology Suggestive of DILI and Alternate Diagnoses

A total of 50 patients with histological features suggestive of DILI were attributed to other causes by the treating physician. In 18 cases, the finding of an alternate condition which excluded a diagnosis of DILI was noted. Acute cellular rejection and systemic infection

were the most was the most common etiologies. recurrent disease with hepatitis C, chronic ductopenic rejection, and biliary stricture were the other major diagnostic categories (Table 5). In 8 cases (16%), an indeterminate cause of acute liver injury was assigned by treating providers because of histological findings that were considered atypical for known causes of allograft dysfunction such as acute cellular rejection.. Notably, we identified 13 (26%) cases where histological changes were compatible with DILI in the absence of other competing causes yet no offending agent was identified or implicated in the medical record.

Discussion

The lack of objective confirmatory diagnostic tests coupled with the highly variable clinical presentation of DILI can often lead to a delay in recognition. In this single center investigation of liver transplant recipients, we have uniquely applied a set of minimum diagnostic elements to improve the accuracy for identifying patients with DILI (9). From a cohort of 1689 LT recipients over a 25 year span, we identified 29 patients with evidence for DILI. As seen with DILI affecting the native liver, over 50% of individuals with DILI after LT were women. While a significant proportion of individuals with DILI underwent LT for PSC, the frequency of this and other indications was not statistically different when compared to LT recipients who di not have DILI. The majority of cases occurred within 6 months of LT, with nearly 25% of cases occurring after 1 year. Jaundice was a presenting feature in 24% of cases, with cholestatic liver enzyme profiles observed in nearly one-half of cases. The majority of our cases were categorized as mild in severity using criteria developed by the NIH Drug-Induced Liver Injury Network (12). The most common agent causing DILI within 90 days of LT was trimethoprim – sulfamethoxazole given for PCP prophylaxis, while a number of other agents were responsible for later cases. As seen with DILI in native livers, the histological spectrum of findings varied but could be grouped into cholestatic and necroinflammatory processes. Furthermore, there was no significant correlation between R values and histological findings in DILI cases as has been recently reported in non-transplant patients (4). The vast majority of patients with DILI improved following drug discontinuation.

These results are in contrast to findings from recent studies of DILI after LT. In a study by Zhenglu et al (8), the authors identified 131 patients with DILI after LT over a 6 year period. In their experience, the majority of DILI episodes occurred within 30 days of LT (44%) which contrasts with our experience where 58% of cases occurred after 90 days from LT. Furthermore, Zhenglu et al. report antifungal agents as the most common class of offending agents (29%) where antibiotics were the most common cause of DILI in our group (48%). However, the criteria used for assessing DILI were not as clearly specified as the minimum diagnostic elements used for this study. Furthermore, an estimated 86% of liver biopsies described hepatocyte fatty change in contrast to 13% of biopsies in our cohort.

The time to onset or latency of DILI is generally difficult to identify based on multiple factors. Uncertainty about timing of initial or repeat medication use, development of symptoms, and delay in obtaining serum liver enzyme tests account for the problems in attributing acute liver injury to DILI. The time to onset may also be difficult to assess because medications can be stopped and re-started or given in several courses or at various doses (4,5). Based on close monitoring with laboratory testing every 1-2 weeks for the first 12 months after LT, a potential advantage in early detection of allograft dysfunction is recognized should the cause of injury ultimately be from DILI. This would also explain, in part, why over 80% of cases were mild to moderate in clinical severity as drug withdrawal could be initiated before further liver dysfunction ensued. However, severe involvement still occurred in 20% of cases

For clinical purposes, there remains no single diagnostic test that can help confirm a diagnosis of DILI. The R ratio is an index which compares the ratio of serum ALT to alkaline phosphatase with respect to their upper limits of normal (i.e. R ratio = (ALT/ULN)/(alkaline phosphatase/ULN) (13). An R ratio ≥ 5 denotes hepatocellular injury while an R ratio ≤ 2 denotes cholestatic injury. Ratios between 2 and 5 are categorized as mixed. However, the usefulness of the R ratio has recently been questioned when laboratory tests and histology are not obtained close in time. Among 192 patients with DILI attributed to a single agent, the R ratio using initial versus peak values demonstrated variation in the classification of hepatocellular (57% vs 45%), cholestatic (22% vs 37%), and mixed (21% vs. 17%) injury patterns (4). Discordance between histology findings and R ratio calculations using initial laboratory tests occurred in 63% of our cohort as well. This underlies the importance of identifying the timing of medication use and degree of serum biochemical abnormalities as indicators for suspecting DILI.

The frequency of individuals experiencing DILI who underwent initial LT for PSC was 28% as compared to the overall proportion of initial LT for PSC at our center (8%). Among non-LT recipients, however, there is little to no documentation in the literature suggesting that PSC may be a risk factor for DILI. Furthermore, it is uncertain whether other autoimmune liver disease such as primary biliary cirrhosis or autoimmune hepatitis pose an increased risk for DILI. The possibility of PSC is certainly in the differential diagnosis of unexplained cholestatic hepatitis, but is clarified after performing cholangiography or liver biopsy to exclude typical or small duct PSC. In our cohort, we did not find evidence for recurrent PSC using strict criteria in patients with an original diagnosis of PSC whose elevated serum liver tests were attributed to DILI.

Trimethoprim-sulfamethoxazole, which is used after LT to prevent *Pneumocystis carinii* pneumonia, was the most common single agent implicated for DILI in our cohort. The potential for hepatotoxicity with this drug has been known for decades, and other side effects reported with its use include skin rash and cytopenia (14,15). The pattern of trimethoprim-sulfamethoxazole hepatotoxicity is variable, but it is usually characterized by cholestasis or a mixed hepatocellular-cholestatic reaction (17). Vanishing bile duct syndrome has also been recently reported (18) although this was not a prominent feature in our cases. Notably, these cases presented with DILI within the first 90 days after LT which is typically when PCP prophylaxis is used.

Immunosuppressive agents such as azathioprine, cyclosporine, and tacrolimus have also been implicated as causative agents for DILI. Several reports have described DILI in association with azathioprine including the development of nodular regenerative hyperplasia (18,19). Cholestatic liver injury has been associated with tacrolimus, and may improve with dose reduction (3,20). Treating physicians in our study also recognized the development of liver injury with azathioprine, cyclosporine, and tacrolimus after exclusion of known etiologies of liver allograft dysfunction. Sirolimus has also been associated with DILI yet reports of jaundice or strict exclusion of other causes of liver injury have not been uniform in the literature (21).

We identified 50 patients in our study with histological features suggestive of DILI but explained by more common etiologies of allograft dysfunction after LT. It should be noted that several cases were found to have zone 3 centrilobular necrosis on liver histology concerning for an atypical presentation of acute cellular rejection. Although potentially reversible conditions such as ischemia or adverse drug reactions are causes of centrilobular necrosis, its presence in liver allografts has been associated with an increased risk for acute cellular ejection, chronic ductopenic rejection, and occasionally allograft failure (22-25). For example, we identified 7 patients who underwent multiple liver biopsies after LT with

results alternating between acute cellular rejection and centrilobular changes suggesting drug-induced liver injury. In most cases, initiation of systemic corticosteroid therapy and/or increasing chronic immunosuppression was performed when zone 3 centrilobular necrosis was found at our institution. However, there may be some patients with centrilobular necrosis from DILI who receive corticosteroids for a presumed diagnosis of acute cellular rejection and have improvement in serum liver enzymes and histology. Nonetheless, it remains advised to assume that centrilobular necrosis should be treated with enhanced immunosuppressive therapy to prevent adverse graft outcomes.

The absence of poor clinical outcomes following DILI in LT recipients is important. As the frequency of immunological causes of graft loss and mortality have declined, other causes have emerged as increasingly important in defining long-term outcomes after LT. Cardiovascular disease, contributed to hypertension and dyslipidemia, has emerged as the second most common late cause of mortality and graft loss following liver transplantation (26), with new data demonstrating metabolic syndrome (MS) in 5.4% of patients before and 51.9% after LT (27). Therefore, pharmacological therapies for hypertension or dyslipidemia etc., e.g. with statins or ACE inhibitors, should not be routinely avoided based on concerns regarding their potential for causing DILI.

Our study identified a number of limitations. The diagnosis of DILI was made retrospectively by two authors (SS, JAT) after applying diagnostic criteria. Therefore, cases were re-adjudicated after taking into consideration additional data from the medical record that was available during follow-up. Future studies should incorporate a panel of experts to adjudicate potential DILI cases prospectively. The search strategies we employed were based on terms that were specific for DILI. In turn, we identified cases where changes in liver histology and serum liver enzyme profiles were highly suggestive of DILI. Patients with DILI in the absence of jaundice/hyperbilirubinemia, or those who did not require liver histology because of rapid improvement in serum liver enzymes following drug discontinuation, could have been missed. Given the retrospective nature of the study, our ability to assess causality for specific agents temporally associated with DILI was also limited as other drugs not mentioned in the medical record could have been involved. However, many centers (including ours) require patients to disclose any new medications being prescribed to them and so the likelihood of unknown prescription or non-prescription agents seems low.

In conclusion, the presence of DILI among liver transplant recipients at our center was approximately 2% when applying strict diagnostic elements. As the clinical presentation of DILI after LT is similar when compared to general population, a high index of suspicion should be retained when unexplained allograft dysfunction is identified without recognition of common etiologies despite extensive testing including liver biopsy.

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Abbreviations

DILI	drug-induced liver injury
LT	liver transplantation
PSC	primary sclerosing cholangitis
CCA	cholangiocarcinoma

HLA	human leukocyte antigen (HLA)
HCV	hepatitis C

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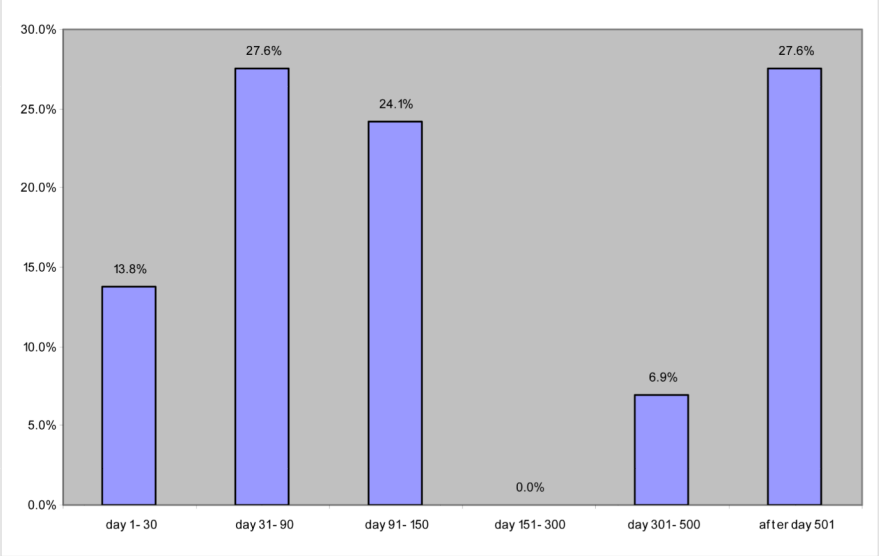

Figure 1.
Frequency of DILI by time period after liver transplantation.

Table 1
Minimal Elements for Reporting Drug-Induced Liver Injury

(Reprinted with permission from Agarwal VK, McHutchison JG, Hoofnagle JH; Drug-Induced Liver Injury Network. Important elements for the diagnosis of drug-induced liver injury. Clin Gastroenterol Hepatol 2010;8:463-70).

Patient sex and age
Drug and its dose
Primary disease (for which drug was prescribed)
Concomitant diseases (with special mention of heart failure or episodes of hypotension, sepsis, or receipt of parenteral nutrition)
Pertinent past medical history (including previous exposure to drug, previous reaction to drug or other drugs, history of liver disease, and risk factors for liver disease)
History of alcohol use
Dates of start and discontinuation of therapy (or time from onset of event)
Symptoms
Date of onset
List of pertinent symptoms (fatigue, weakness, nausea, anorexia, abdominal pain, dark urine, jaundice, pruritus, rash, and fever)
Pertinent physical findings at the time of presentation (with special mention of whether or not there is fever, rash, jaundice, hepatic tenderness, or signs of chronic liver disease)
Medication history (other medications taken in the 3 months before onset of liver injury with dose, generic name, and duration)
Laboratory tests
Date or time of first abnormal laboratory test result
Laboratory test results from before drug exposure (specifically liver tests)
Initial laboratory results at presentation (bilirubin, ALT, AP, INR, or PT, and eosinophil count or percentage)
Laboratory results needed to exclude other causes (IgM anti-HAV, IgM anti-HBc, HBsAg, anti-HCV, HCV RNA, and ANA)
Course of serum bilirubin, ALT, AP, and INR levels (preferably in a table with entries dated from time of starting and stopping the drug and until resolution)
Imaging studies (abdominal ultrasound, CT, or MR)
Liver histology results (if obtained and date of procedure in relation to episode of drug-induced liver injury)
Whether rechallenge with the same medication was performed and, if so, results of the challenge

ANA, antinuclear antibody; AP, alkaline phosphatase; CT, computed tomography; HAV, hepatitis A virus; HBc, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; Ig, immunoglobulin; INR, international normalized ratio; MR, magnetic resonance; PT, prothrombin time.

Table 2
Demographic and Clinical Features of Definite DILI Cases

Age, mean ± SD (y)	52 ± 12.1
Proportion aged ≥ 65 years (%)	14
Female (%)	52
Days of using offending drug, median	57.5
Liver biochemistries, values at DILI onset (mean ± SD)	
ALT (U/L)	204±263
AST (U/L)	108±237
Alkaline phosphatase (U/L)	469±689
TB (mg/dL)	1.9±10.3
Indication for LT	
Primary sclerosing cholangitis (%)	28
Cholangiocarcinoma	14
Hepatocellular carcinoma	14
Other	14
Metabolic liver disease	10
Primary biliary cirrhosis	7
Hepatitis C	3
Alcohol	3
Autoimmune hepatitis	3
Hepatitis B	3
Clinical features (%)	48
Gastrointestinal symptoms	31
Jaundice	24
Pruritus	10
Fever	10
Rash	3
Histological Pattern of Liver injury (%)	
Hepatocellular	43
Cholestatic	32
Mixed	11
Lobular hepatitis	11
Atypical	3
Severity of DILI (%)	
Mild	71
Moderate	21
Moderate-severe	4
Severe	4
Fatal	0

Donor age , mean ± SD (y)	36±19,5
Female donor (%)	56

Table 3

Implicated Agents in DILI

Single agent DILI	Part of multi-agent DILI
Trimethoprim-Sulfamethoxizole	Medroxyprogesterone
Tacrolimus	Acyclovir
Azathioprine	Daptomycin
Metoprolol	Ertapenem
Paroxetine	Cotrimoxazole
Amantadine	Ursodiol
Nafcillin	Ergotamine
Pravastatin	Trimethaphan
Fluconazole	Gabapentin
Clarithromycin	Gemfibrozil
Herbal tea	Allopurinol
	Mesalamine
	Amitriptyline
	Clonidine
	Nystatin
	OBDS
	Vitamin K
	Pravastatin
	Ezetimibe
	Omeprazole

Table 4

Definitions for Severity of DILI

(Reprinted with permission from Fontana RJ, Watkins PB, Bonkovsky HL, Chalasani N, Davern T, Serrano J, Rochon J; DILIN Study Group. Drug-Induced Liver Injury Network (DILIN) prospective study: rationale, design and conduct. Drug Saf 2009;32:55-68.)

Grade	Definition
Mild	Patient has elevation in ALT and/or alkaline phosphatase levels but total serum bilirubin is <2.5 mg/dL *and* INR is <1.5
Moderate	Patient has elevation in ALT and/or alkaline phosphatase levels *and* serum bilirubin is >2.5 mg/dL or INR is > 1.5
Moderate-severe	Patient has elevation in ALT, alkaline phosphatase, bilirubin and/or INR Ievels and patient is hospitalized or an ongoing hospitalization is prolonged because of DILI
Severe	Patient has elevation in ALT and/or alkaline phosphatase levels and total serum bilirubin is 2.5 mg/dL or greater and there is at least one of the following: (i) hepatic failure (INR >1.5, ascites or encephalopathy); (ii) other organ failure believed to be due to DILI event
Fatal	Patient dies or undergoes liver transplantation because of DILI event

INR, international normalized ratio; ALT, alanine aminotransferase; DILI, drug-induced liver injury

Table 5
Alternate Diagnoses in Cases with Possible DILI on Liver Histology

Alternative Clinical Diagnoses	(%)
Acute cellular rejection	18
Infection	18
Recurrent HCV infection	9
Chronic ductopenic rejection	7
Biliary stricture	6
Indeterminate/unknown	16
Compatible with DILI yet no offending agent recognized	26