Drug-Induced Acute Liver Failure: Results of a U.S. Multicenter, Prospective Study

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Acute liver failure (ALF) due to drug-induced liver injury (DILI), though uncommon, is a concern for both clinicians and patients. The Acute Liver Failure Study Group has prospectively collected cases of all forms of acute liver failure since 1998. We describe here cases of idiosyncratic DILI ALF enrolled during a 10.5-year period. Data were collected prospectively, using detailed case report forms, from 1198 subjects enrolled at 23 sites in the United States, all of which had transplant services. A total of 133 (11.1%) ALF subjects were deemed by expert opinion to have DILI; 81.1% were considered highly likely, 15.0% probable, and 3.8% possible. Subjects were mostly women (70.7%) and there was overrepresentation of minorities for unclear reasons. Over 60 individual agents were implicated, the most common were antimicrobials (46%). Transplant-free (3-week) survival was poor (27.1%), but with highly successful transplantation in 42.1%, overall survival was 66.2%. Transplant-free survival in DILI ALF is determined by the degree of liver dysfunction, specifically baseline levels of bilirubin, prothrombin time/international normalized ratio, and Model for End-Stage Liver Disease scores. *Conclusion:* DILI is an uncommon cause of ALF that evolves slowly, affects a disproportionate number of women and minorities, and shows infrequent spontaneous recovery, but transplantation affords excellent survival. (HEPATOLOGY **2010;52:2065-2076**)

Abbreviations: ALF, acute liver failure; ALT, alanine aminotransferase; ANA, antinuclear antibody; BMI, body mass index; CAM, complementary and alternative medication; CI, confidence interval; DILI, drug-induced liver injury; FDA, U.S. Federal Drug Administration; INR, international normalized ratio; IQR, interquartile range; MELD, Model for End-Stage Liver Disease; NAC, N-acetylcysteine; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; SD, standard deviation; TMP-S, trimethoprim-sulfamethoxazole; UTSW, University of Texas, Southwestern.

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Idiosyncratic drug-induced liver injury (DILI), has been the major reason for denial of approval, withdrawal from the market, or "black box" warnings for many drugs and complementary and alternative medicines (CAMs), by the U.S. Food and Drug Administration (FDA).[1-4] More than 1100 drugs, herbal remedies, natural products, vitamins, minerals, dietary supplements, and recreational and illicit compounds have been reported to cause DILI[5-7] (albeit, some only occasionally); prevalences are mostly less than 1 in 100,000 to 1 in 10,000 patients, but are occasionally more frequent.[6] Estimates of the burden of DILI vary according to criteria for cohort selection.[8,9] In a population-based study from a rural area in France,[10] the crude global incidence of DILI was 13.9 cases/100,000 population—a rate 16-fold higher than reported to regulatory authorities. Four of 34 (11.8%) patients in that study were hospitalized, and two (5.9%) died.[10] In a 1990s United Kingdom-based survey,[11] DILI requiring specialist referral affected 2.4 cases/100,000 person-years (similar to the 1980s DILI incidence in Denmark[12]), of whom 36/128 (28.2%) were hospitalized, but only one required liver transplantation. DILI is a frequent cause of hepatitis[13] and hospitalization,[11,12] and is implicated in 5%-10% of all patients hospitalized for jaundice,[14,15] accounting for 95% of adverse drug reactions and 14.6% of drug fatalities in Denmark.[12]

Case series of severe idiosyncratic DILI and DILI-induced acute liver failure (ALF) leading to death or liver transplantation have been described[16-19] and reviewed.[20] Since our initial report of ALF in the United States,[21] there has been no overview of ALF caused by nonacetaminophen DILI. The aim of the present study is to identify presenting features, suspect agents, and predictors of outcome in a consecutive cohort of adult idiosyncratic DILI ALF patients.

Patients and Methods

From January 20, 1998 through July 5, 2007, demographic, clinical, and laboratory results were recorded prospectively at enrollment, and imaging, histology, and outcome data were obtained from 1198 subjects meeting entry criteria for ALF at 23 academic centers participating in the National Institutes of Health (NIH)-funded Acute Liver Failure Study Group.[21] All centers had liver transplant services. By definition, ALF patients had coagulopathy (international normalized ratio [INR] $\geq$ 1.5), hepatic encephalopathy (hepatic coma), and $<$26 weeks of illness without apparent chronic liver disease.[21] Written informed consent was obtained from legal next-of-kin. Outcomes within 3 weeks of enrollment were defined as transplant-free (i.e., spontaneous) survival and discharge, liver transplantation, or death.[21] All centers complied with their local Institutional Review Boards' requirements and the Health Insurance Portability and Accountability Act (HIPAA). A few subjects were also enrolled in a prospective study of DILI[19]; those who were treated with n-acetylcysteine (NAC) were enrolled in a prospective trial of NAC for nonacetaminophen ALF.[22]

A careful history of prescription drug, over-the-counter medication, dietary supplements, CAM, and illicit substance use, and comorbid conditions was obtained. Duration of medication use, including timing of initiation and cessation in relation to the onset of symptoms, jaundice, hepatic coma, and study enrollment were recorded. DILI was diagnosed by experienced hepatologists at the local sites. All case report forms were scrutinized at the Central Site (UTSW) and then independently by the principal author (A.R.). DILI was accepted as the cause of ALF if the patient was taking a drug with a strong association with idiosyncratic DILI, in an appropriate time-frame, and if competing causes of ALF were excluded by rigorous evaluation of history, laboratory and imaging findings, and, in some cases, liver biopsy (including explants for transplant recipients). A drug, CAM, or illicit substance was considered "highly likely" to have caused DILI ALF if it was the sole agent or it was taken together with other low-DILI-potential medicines, for a reasonable time prior to presentation. A compound of known hepatotoxicity was considered to be the "probable" cause of DILI ALF if temporal details were not recorded precisely or if other drugs of lesser DILI potential were also taken. A drug was considered a "possible" cause of ALF if it was taken at some unspecified time prior to presentation and there were no other competing causes, or the time course was known but there were other competing drugs and/or comorbidities. DILI was characterized as hepatocellular, cholestatic, or a "mixed" reaction, by calculating the ratio (R) of the relative elevation of alanine aminotransferase (ALT, as a multiple of its upper limit of normal) to the relative elevation of alkaline phosphatase,[19] at enrollment. Model for End-Stage Liver Disease (MELD) scores were also calculated.[23]

Statistical Analysis. Continuous data are presented as means and standard deviations (SDs) if normally distributed, or as medians and interquartile ranges (IQRs) if not. Three-week outcomes were as follows: (1) transplant-free survival, (2) transplantation, and (3) nontransplantation death. Bivariate associations between continuous variables and outcomes were assessed using the Kruskal-Wallis test for overall outcome and Wilcoxon rank-sum for transplant-free survival; results are reported as medians with IQRs. Multiple pairwise comparisons were made with Tukey's procedure, and an overall α-level was determined by Bonferroni's correction for multiple tests. For categorical variables, associations with outcome were assessed via a χ^2 test or Fisher's exact test, as appropriate, and reported as proportions. An association between NAC use and severity of liver disease, defined by coma grade as it pertains to transplant-free survival, was identified *a priori* and assessed with the Cochran Mantel-Haenszel χ^2 test, because an interaction between the two covariates had been identified in the ALF NAC Trial.[22]

Multivariable logistic regression analysis for transplant-free survival was performed on selected baseline variables from the univariate analyses, continuous variables were assessed for linearity in the log-odds with the Loess procedure, and analysis for interaction and colinearity was done for all covariates. The final multivariable model was assessed using the Hosmer-Lemeshow goodness-of-fit test. Statistical significance was defined as a two-sided $P < 0.05$. Analyses were performed using SAS (version 9.1.03; SAS Institute, Inc., Cary, NC).

Results

Demographics and Clinical Features. Of the 1198 ALF subjects, 136 were considered by the site investigator to have DILI; three subjects were subsequently rejected as "indeterminate" cases, leaving 133 (11.1%).

Overall, 94 (70.6%) of the DILI ALF patients were women. The average age of the DILI subjects was 43.8 years ± 14.1 SD (range, 17-73 years). Twenty (15.0%) subjects were ≥60 years, and eight (6.0%) were ≥65 years. A positive alcohol history was obtained in 38 subjects but quantification was only possible in 18, of whom eight admitted to using ≥30 g daily. One patient had chronic hepatitis B and four were treated for human immunodeficiency virus (HIV) infection. The racial/ethnic makeup of the 133 subjects was: white 76 (57.1%); African American 21 (15.8%); Hispanic 20 (15.0%); and 16 (12.0%) others (Supporting Table 1)

On average, the subjects were overweight (median body mass index [BMI], 28.7 kg/m^2; IQR, 24.6-32.8), 43.4% seriously so (BMI ≥ 30), and 17.9% were obese (BMI ≥ 35). At enrollment, shock was uncommon and only 19 (14.2%) subjects had a mean arterial pressure ≤70 mm Hg. The average coma grade was 2.2 ± 1.1; more than two-thirds of the subjects (91; 68.4%) had advanced coma (grade ≥ 2). Peripheral edema was common (43.4% subjects); clinically-detectable ascites was observed in 24.6% of subjects, and deep jaundice was typical.

Laboratory results at enrollment (Supporting Table 2A,B) were widely dispersed. There was mild leukocytosis (mean white blood count, 13.5 × 10^6/μL). White-cell differential counts were recorded in 93 subjects; eight (8.6%) had a relative eosinophilia (≥5%) and 10 (10.8%) had an absolute eosinophilia (≥400/μL). Mean bilirubin was 20.8 mg/dL ± 11.5, but aspartate aminotransferase and ALT were only moderately elevated (medians 551 IU/L and 574 IU/L, respectively). Alkaline phosphatase elevations were modest, albumin was moderately depressed (median, 2.4 g/dL; IQR, 2.1-2.7), and INR was substantially deranged (median, 2.6; IQR, 1.9-4.1). Overall, renal function appeared intact (median creatinine 1.2 mg/dL; IQR, 0.8-2.8) but 60 subjects (45.1%) had some and often severe renal impairment (serum creatinine ≥ 1.5 mg/dL; range, 1.5-9.3; IQR, 2.0-4.3). Marked creatinine elevations were associated with high levels of creatinine kinase but the latter were measured infrequently. MELD scores were high and similar among racial/ethnic groups and genders. Mean MELD score was 33 ± 9.2 (median, 33; IQR, 27-39). DILI was hepatocellular (R ≥ 5) in 98 (77.8%) subjects, a mixed reaction (2 < R < 5) in 12 (9.5%), and cholestatic (R ≤ 2) in 16 (12.6%). Data were missing in seven subjects.

Agents Implicated in DILI ALF. Sixty-one different agents, alone or in combination, were thought to cause DILI ALF (Table 1A-C). Causality assessment, by expert opinion, indicated that a selected agent was highly likely in 108 (81.1%), probable in 20 (15.0%), and only possible in five (3.8%) cases. Four cases were considered only possible due to use of many compounds, unknown temporal associations, comorbid conditions, or use of agents of low DILI potential; the fifth case had taken atorvastatin as the only medication with DILI potential, for 36 months. In 27 (20.3%) cases, only one drug was used, including nine isoniazid cases. In three cases, a combination of two to four antituberculosis drugs (isoniazid, rifampin, pyrazinamide, and ethambutol) were the only medications used. The remaining 103 (77.4%) cases were taking several and sometimes many other agents besides the prime suspect(s), including drugs of varying hepatotoxic potential (Table 2).

Antimicrobials were most commonly responsible for DILI ALF (Table 1A), among which antituberculosis therapies predominated. Isoniazid was the sole antituberculosis drug in 15 cases, and in six cases in combination. Sulfur drugs frequently caused ALF, especially trimethoprim-sulfamethoxazole (TMP-S) alone (nine cases); this agent was also implicated in combination with azithromycin, a statin, and/or antiretroviral compounds. Nitrofurantoin was implicated 12 times. Terbinafine and azole antifungal drugs were relatively common, but antiretroviral drugs were infrequent. CAM, nonprescription medications, dietary supplements, weight loss treatments, and illicit substances—several of which carry FDA warnings[24]—were responsible for 14 (10.6%) cases. Of the neuropsychiatric drugs, phenytoin use (eight cases) was frequent, along with other antiepileptics (n = 5), and psychotropic drugs (n = 4). Halogenated anesthetic hepatotoxicity occurred twice. Disulfiram for alcoholism, and propylthiouracil for thyrotoxicosis, accounted for nine cases each. Bromfenac was implicated in four cases, whereas other nonsteroidal anti-inflammatory drugs (NSAIDs), biological agents, and leukotriene inhibitors were infrequent hepatotoxins. One patient treated with gemtuzumab following bone marrow transplantation developed sinusoidal obstruction syndrome.

Fifteen subjects were taking statins, in four of whom another drug was the likely cause of DILI ALF (TMP-S, nitrofurantoin, and cefopime, respectively, and one subject was treated with amoxicillin-clavulanic acid followed by amoxicillin). Cerivastatin was used in two cases, simvastatin in two (alone or with ezetemibe), and atorvastatin in two. In one subject taking nitrofurantoin, atorvastatin was changed after 1 month to simvastatin, which was used for 2 months. In another, combination simvastatin/ezetimibe was used

Table 1. Causes of DILI ALF

A. Antimicrobial Agents	Cases (n)
Antituberculosis drugs	25
Isoniazid alone	15
Isoniazid combined with 2 of 3: rifampin, pyrazinamide, and ethambutol	6
Rifampin and pyrazinamide with or without ethambutol	3
Dapsone	1
Sulphur-containing drugs	12
Trimethoprim/sulfamethoxazole alone	6
Trimethoprim/sulfamethoxazole in combination with azithromycin, statin and/or antiretroviral drugs	3
Sulfasalazine	3
Other antibiotics	19
Nitrofurantoin alone	11
Nitrofurantoin with a statin	1
Amoxicillin (2), doxycycline (2), ciprofloxacin (1), clarithromycin (1), cefepime (1)	7
Antifungal agents	6
Terbinafine	3
Itraconazole	1
Ketaconazole alone	1
Ketaconazole with ezetemibe	1
Antiretroviral drugs	4
Stavudine with didanosine	2
Lamivudine with stavudine and nelfinavir	1
Abacavir	1
B. CAMs, and Illicit Substances, Neuropsychotropic Drugs, and Anesthetics	**Cases (n)**
CAMs and illicit substances	14
Unspecified herbal preparations	3
Usnic acid	2
Thermoslim (contains saw palmetto)	1
Herbal mixture (contains blue-green algae)	1
Ma-Huang	1
Horny goat weed	1
Black cohosh	1
Hydroxycut	1
Uva-ursi	1
Cocaine	1
Ectasy	1
Antiepileptic drugs	11
Phenytoin	8
Divalproic acid	2
Carbamazepine	3
Psychotropic agents	4
Quetiapine	1
Nefazodone	1
Fluoxetine	1
Venlafaxine	1
Anesthetics	2
Halothane	1
Isoflurane	1
C. Antimetabolites and Enzyme Inhibitors, Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), Biological Agents, Statins, and Other Drugs	**Cases (n)**
Antimetabolites and enzyme inhibitors	11
Disulfiram	4
Propylthiouracil	5
Allopurinol	1
Melphalan	1
NSAIDs	7
Bromfenac	4
Diclofenac	2
Etodolac	1
Biological agents and leukotriene inhibitors	4
Gemtuzumab	1
Zafirlukast	1
Interferon β	1
Bacille-Calmette-Guérin (BCG)	1
Statins and Ezetemibe*	6
Cerivastatin	2
Simvastatin ($\pm$ezetimibe)	2
Atorvastatin	2
Other drugs	8
Troglitazone	4
Oxyiminoalkanoic acid derivative	1
Methyldopa	2
Hydralazine	1

* Four other statin cases: one subject took pravastatin for 6 months, and then took TMP-S for 2 weeks; two subjects each took nitrofurantoin for 1 year, and received either atorvastatin (1 month) followed by either simvastatin (2 months) or with simultaneous nateglinide (1year); one subject took simvastatin and nitrofurantoin simultaneously for 1 year; and one subject was treated with both TMP-S and simvastatin/ezetemibe for 9 and 10 days, respectively.

with TMP-S, each for 9-10 days, whereas the remaining three statin cases were treated simultaneously with TMP-S, nateglinide, or nitrofurantoin, respectively. Suspect DILI ALF agents were used from 1-2 weeks, up to 8 months. Notable exceptions were the single exposures with halothane and isoflurane; nitrofurantoin use was as brief as a month to upward of 1-3 years; single cases used fluoxetine for 15 months and divalproic acid for 3 years, respectively. Statins causing DILI ALF were taken for a month or two, to upward of 3 years. Troglitazone (n = 4) and an experimental oxyiminoalkanoic acid derivative (TAK 559), were the only hypoglycemic compounds, and hydralazine and methyldopa (one each) the only antihypertensives.

DILI-causing agents were discontinued before any recorded symptom in 25 cases (18.8%) or after the onset of symptoms but before jaundice in 19 (14.3%). Most subjects (86; 64.7%) did not stop until or after jaundice supervened. There were five rechallenge cases: antituberculosis drugs (2), amoxicillin-clavulanic acid followed by amoxicillin (1), usnic acid (1), and sequential sulfur-containing drugs (1). One usnic acid case became evident only after she underwent transplantation, because her husband then developed usnic acid hepatitis.

Immunoallergic Drug Reactions. Rash and/or eosinophilia occurred in 11 and 10 subjects, respectively—only two had both. Rashes occurred with phenytoin (4), antituberculosis or sulfur drugs (3), and with abacavir, allopurinol, atorvastatin, and diclofenac, respectively. Stevens-Johnson syndrome was caused

Table 2. Compounds Taken by ALF Subjects, In Addition to Presumed DILI Causative Agents

Acetaminophen	Famotidine	Nateglinide
Acyclovir	Fentanyl	Nelfinavir*
Albendazole	Fludarabine	Nitroglycerin
Albuterol	Flunisolide	Nortriptyline
Albuterol/ipratropium	Fluoxetine*,†	Omeprazole
Alendronate	Fexofenadine	Oral contraceptive steroids, various
Alprazolam	Fluticasone	Oxcarbazepine
Amantadine	Furosemide	Oxybutynin
Amlodipine†	Gabapentin†	Oyst-Cal
Amlodipine/benazepril	Garlic	Pantoprazole
Amoxicillin*,†	Glipizide†	Paroxetine
Amoxicillin/clavulanate†	Glucosamine	Penicillin G
Aspirin	Guaifenesin	Pentosan polysulfate
Atenolol	Haloperidol	Peptaline
Atorvastatin	Hogworts	Perphenazine
Azithromycin†	Hydrochlorothiazide	Phenytoin*,†
Baclofen	Hydrocodone	Pioglitazone
Benztropine	Hydrocodone/ibuprofen	Prednisone
Breast Enhance	Hydroxychloroquine*	Primidone
Buchu leaf (*Agathosma betulina*)	Hydroxyurea	Progesterone
Bupropion†	Hydroxyzine	Promethazine†
Buspirone	Ibuprofen†	Propoxyphene
Butalbital/acetaminophen/aspirin/caffeine	Insulin	Propoxyphene/acetaminophen
Calcium carbonate	Irbesartan	Propranolol
Carbamazepine*	Isotretinoin	Pseudoephedrine
l-Carnitine	IVIG	Quinine
Carvedilol	Kava-Kava	Ramipril
Cefprozil	Ketoconazole	Ranitidine†
Ceftriaxone†	Ketoprofen	Riboflavin
Cellocal	Lactulose	Rifabutin
Cetirizine	Lamivudine	Risperidone
Chinese Module Solution	Lansoprazole†	Rizatriptan
Cholestyramine	Levetiracetam	Rosiglitazone
Cimetidine	Levothyroxine	Senna
Ciprofloxacin*,†	Lisinopril	Sertraline†
Citalopram	Lithium	Stavudine*
Clarithromycin	Lorazepam	Theophylline
Clindamycin†	Losartan	Thiamine
Clonazepam	l-Lysine	Topiramate†
Clopidogrel	Marijuana	Tramadol
Cyclophosphamide†	Medroxyprogesterone	Trazodone
Diphendydramine	Megaman vitamins	Triamterene
Divalproate*	Metabolife	Triamterene/hydrochlorothiazide
Docusate sodium	Metformin	Trimethobenzamide
Echinacea	Methylphenidate†	Trimethoprim-sulfamethoxazole*,†
Enalapril	Methylprednisolone	Valsartan†
Enoxaparin	Metoclopramide	Valsartan/HCTZ
Ephedrine/caffeine/aspirin	Metoprolol†	Varenicline
Erythropoietin	Mirtazapine	Venlafaxine*
Escitalopram†	Montelukast	Verapamil†
Estradiol†	Multivitamins	Vitamin C
Estrogen, conjugated	Myrrh	Vitamin K
	Naproxen	Zonisamide

* Implicated in DILI ALF in other patients in this study.

† Implicated in DILI, alone or in combination, in the study by Chalasani et al.[19]

either by sulfasalazine or phenytoin, respectively; a subject receiving dapsone suffered skin desquamation. Eosinophilia was commonest with antituberculosis drugs (five cases), but also occurred with abacavir, phenytoin, disulfiram, interferon β, and divalproic acid. Neither cholestasis nor mixed reactions appeared characteristic of any therapeutic class, as many drugs that cause hepatocellular injury were used in these 28 cases (Table 3).

Autoantibodies were found in 50 of 79 subjects tested, with titers >1:40 in 19; two had anti-smooth muscle antibodies (1:320 and 1:1280), and 17 were antinuclear antibody (ANA)-positive (1:80 to 1:640). None had significant anti–mitochondrial antibody positivity. In 13 of 19 strongly auto-antibody–positive subjects for whom liver histology was available, microscopy did not show autoimmune features; 12 had massive or submassive necrosis and in one there was extensive microvesicular steatosis. The anti–smooth muscle antibody–positive subjects took nitrofurantoin or sulfasalazine. High ANA titers were seen in DILI cases attributed to Ma-huang, nefazodone, fluoxetine, propylthiouracil, bromfenac, cerivastatin, simvastatin, troglitazone, and hydralazine (titers of 1:80-1:320), respectively; in three cases each of antituberculosis drugs (1:160-1:320) and nitrofurantoin (1:80-1:640), respectively; and two cases of ketaconazole (1:320). No patient with autoantibodies had a rash or eosinophilia. Overall, 38 (28.6%) subjects had some hypersensitivity manifestation.

Outcomes. Only 36 (27.1%) of the subjects recovered spontaneously without liver transplantation (Tables 4 and 5). Of the remaining 97 subjects, 56 (42.1% of the cohort) underwent liver transplantation with excellent results within the study 3-week capture period (four deaths, 92.9% survived), giving an overall survival of 66.2% (88 subjects). Another 17 subjects were listed but died without receiving transplantation, i.e., 23.3% wait-list mortality. Whereas 73 (54.9%) subjects were listed for liver transplantation, 24 (18.0%) were not, because of medical, psychosocial, or other contraindications. Nontransplant mortality was 30.8% (41 subjects).

By univariate analysis, the baseline factors significantly associated with a good outcome were lower coma grades, bilirubin, INR, creatinine, and MELD scores, but not age, gender, BMI, blood pressure, drug class, type of DILI reaction, or liver enzyme elevation (Table 4). Subjects undergoing transplantation were younger on average by 7 to 9 years, than those who recovered spontaneously or died, respectively (Table 4). Among the 20 subjects ≥60 years and eight ≥65

Table 3. Drugs Implicated in Mixed (2 < R < 5) and Cholestatic (R ≤ 2) Reaction DILI ALF

	Cases (n)
Mixed reactions	12
Isoniazid (alone)	1
Isoniazid, ethambutol, and pyrazinamide (combined)	1
Rifampin, ethambutol, and pyrazinamide (combined)	1
Nitrofurantoin	3
Trimethoprim/sulfamethoxazole	1
CAMs, illicit drugs, etc.	1
Fluoxetine	1
Bromfenac	1
Zafirlukast	1
Interferon β	1
Cholestatic reactions	16
Isoniazid (alone)	2
Trimethoprim/sulfamethoxazole	1
Cetopime	1
Ketoconazole	1
Phenytoin	1
Propylthiouracil	2
Melphalan	1
Bromfenac	1
Diclofenac	1
BCG	1
Cerivastatin	2
Atorvastatin	1
Methyldopa	1

Abbreviation: R, ratio of relative elevation of ALT to relative elevation of alkaline phosphatase.[19]

years, transplant-free survival (six out of 20, or 30%, and two out of eight, or 25%, respectively) was comparable to the whole cohort. Few older subjects underwent transplantation (four of 20 ≥60 years, and one of eight ≥65 years) but all survived. Consequently, nontransplant death rates were high in this older subset (50% ≥60 years and 63% ≥65 years), compared to the whole cohort (30.9%).

Transplant-free survivors were significantly less jaundiced (median bilirubin 12.6 mg/dL; IQR, 5.2-24.1) than those who died or underwent transplantation (20.5 and 23.3 mg/dL, respectively). Subjects who did not undergo transplantation who died had worse renal compromise (median creatinine 2.1 mg/dL) than survivors who did not undergo transplantation (1.1 mg/dL) and subjects undergoing transplantation (1.0 mg/dL). When transplant-free survival was compared to transplantation and death combined (Table 5), creatinine did not differ between the groups. The worst INRs were seen in transplant subjects. Though all MELD scores were high, median MELD scores were lowest for the transplant-free survivors (29.0), intermediate for transplant recipients (32.5), and highest for the nontransplant deaths (36.0), but not statistically so. NAC treatment was slightly more frequently associated with spontaneous survival (38.6%) than with transplantation (34.1%) and nontransplantation death (27.3%), respectively. Transplant-free survival (compared to transplantation or death) was greater with (38.6%) than without NAC (21.4%), without regard to coma grade (Table 5). There were too few subjects to permit conclusions about the interaction between NAC and coma grade, as reported in the NAC trial.[22]

Whether the subjects discontinued the suspect agent before or after symptoms and/or jaundice occurred did not affect outcome. We also examined the relationship between illness duration and survival, because outcome has been inversely related to the tempo of development of ALF.[25] The intervals between onset of symptoms and stage 1 coma (or stage 2 coma; data not shown), or between jaundice and stage 1 coma, respectively, were shorter in transplant-free survivors than in those who underwent transplantation, those who died, and those who underwent transplantation or died, respectively (Table 4 and 5), but not statistically significant by univariate (Table 4) or multivariate (Table 5) analysis.

Multivariable Logistic Regression Analysis. Severity of coma, MELD score, and NAC use were entered into a multivariable logistic regression model. MELD met the requirements for linearity in the log odds for rate of transplant-free survival, and neither colinearity nor interaction was present among the covariates. Both MELD score (odds ratio [OR], 0.94; 95% confidence interval [CI], 0.89-0.99; $P = 0.01$) and coma severity (OR, 0.33; 95%CI, 0.14-0.79; $P = 0.01$) predicted poor outcomes; however, NAC use was no longer predictive (OR, 1.89; 95%CI, 0.79-4.51; $P = 0.15$); the model fit was adequate by the Hosmer-Lemeshow goodness-of-fit test ($P = 0.88$).

Discussion

This study prospectively explores the causes and consequences of the most serious form of DILI, namely ALF. DILI ALF is characterized by deep jaundice, fluid retention, advanced coagulopathy, and coma (but only moderate elevations of aminotransferases), indicating a slowly evolving or "subacute" condition. This biochemical profile of DILI ALF contrasts with acetaminophen-induced and most other identifiable causes of ALF, which show much higher aminotransferases[21,26,27] and, in the case of acetaminophen, much less hyperbilirubinemia.[26] One-quarter of DILI ALF subjects exhibited an immunoallergic reaction, i.e., rash, eosinophilia, or autoantibody positivity. Despite polypharmacy, it was relatively easy to decide which drug or group of drugs was the likely culprit. The

Table 4. Outcome of DILI ALF: Transplant-Free Survival versus Transplantation versus Death

Variable	Spontaneous Survival (n = 36) (%)*,†	Transplanted (n = 56) (%)*,†	Nontransplant Death (n = 41) (%)*,†	P
Age (years)	47 (30.5-54.5)	40.0 (31.5-49.5)	49.0 (35.0-59.0)	0.07‡
Race				0.34§
White	24 (31.6)	31 (40.1)	21 (27.6)	
Black	3 (14.3)	7 (33.3)	11 (52.4)	
Hispanic	5 (25.0)	11 (55.0)	4 (20.0)	
Other	4 (25.0)	7 (43.8)	5 (31.3)	
Gender				0.20
Male	12 (30.8)	12 (30.8)	15 (38.4)	
Female	24(25.5)	44 (46.8)	26 (27.7)	
Drug class‖				0.98
Antituberculosis	7 (28.0)	10 (40.0)	8 (32.0)	
Sulphur-containing	3 (27.3)	4 (36.4)	4 (36.4)	
Nitrofurantoin	3 (27.3)	5 (45.4)	3 (27.3)	
Antifungals	1 (20.0)	2 (40.0)	2 (40.0)	
CAMs, illicit drugs, etc.	3 (21.4)	7 (50.0)	4 (28.6)	
Antiepilepsy	5 (45.5)	5 (45.5)	1 (9.0)	
Antimetabolites	2 (18.2)	5 (45.5)	4(36.4)	
Statins	3 (30.0)	3 (30.0)	4 (40.0)	
R value				0.26
Hepatocellular	26 (26.5)	45 (45.9)	27 (27.6)	
Mixed	2 (16.7)	4 (33.3)	6 (50.0)	
Cholestatic	7 (43.8)	4 (25.0)	5 (31.2)	
Discontinue time				0.29
Before onset of symptoms	7 (28.0)	10 (40.0)	8 (32.0)	
At or after onset of symptoms, and before jaundice	9 (47.4)	7 (36.8)	3 (15.8)	
At or after onset of jaundice	20 (23.3)	36 (41.8)	30 (34.9)	
Coma grade				0.001
Grade 1	20 (47.6)	13 (31.0)	9 (21.4)	
Grade 2	10 (23.8)	23 (54.8)	9 (21.4)	
Grade 3	5 (18.5)	12 (44.4)	10 (37.1)	
Grade 4	1 (4.6)	8 (36.4)	13 (59.1)	
Interval (days)				
Onset to coma	12.0 (6.0-24.0)	18.0 (9.0-25.0)	15.5 (8.5-32.5)	0.52
Jaundice to coma	6.0 (0.0-14.0)	11.0 (4.0-21.0)	9.5 (5.5-17.0)	0.89
NAC				0.12
Yes	17 (38.6)	15 (34.1)	12 (27.3)	
No	19 (21.4)	41 (46.0)	29 (32.6)	
BMI	29.0 (25.1-34.4)	29.0 (24.6-32.5)	27.0 (23.8 -32.5)	0.73
MAP	91.0 (75.0-96.5)	87.5 (79.0-96.0)	82.0 (74.0-93.0)	0.53
Bilirubin (mg/dL)	12.6 (5.2-24.1)	20.5 (13.0-29.8)	23.3 (19.6-30.0)	<0.001
INR	2.4 (1.8-2.7)	3.1 (2.3-4.5)	2.6 (1.9-3.9)	0.0006
Creatinine (mg/dL)	1.1 (0.8-3.1)	1.0 (0.7-1.9)	2.1 (0.9-3.6)	0.03
AST	588.5 (389.0-1419.5)	551.0 (241.0-1153.0)	623.0 (267.0-1065.0)	0.52
ALT	784.5 (258.0-2013.5)	616.0 (268.0-1419.0)	387.0 (220.0-1262.5)	0.31
Alkaline phosphatase	166.0 (130.0-239.0)	165.5 (112.0-220.0)	164.0 (119.0-260.0)	0.57
MELD score	29.0 (23.0-36.0)	32.5 (27.0-39.0)	36.0 (29.0-43.0)	0.007

Abbreviations: NAC, n-acetylcysteine; MAP, mean arterial pressure.

* Values are medians with interquartile ranges in parentheses for continuous variables, and numbers of patients with percentages in parentheses for categorical ones.

† Number of subjects are also shown as a percentage for each variable.

‡ Continuous variables analyzed by Kruskal-Wallis test.

§ Categorical variables analyzed by chi-square or Fisher's exact test.

‖ Only drug classes (or individual drugs) taken by six subjects or more were included in the analysis.

most common causes of DILI ALF were antimicrobials, but neuroactive drugs, various CAMs, illicit substances, and statins were frequently implicated. The outcome of DILI ALF is predicted by the degree of liver dysfunction—as judged by the severity of coma, hyperbilirubinemia, and coagulopathy—but not by the class of drugs, drug injury pattern, age, gender, obesity, or timing of cessation of drug use. When transplant-free recovery from DILI ALF is combined with the excellent results of liver transplantation, overall survival approaches 70%.

In the current study, the high female predominance is similar to the gender imbalance seen in DILI ALF in Spain,[28] in acetaminophen-induced ALF in Sweden,[29]

Table 5. Outcome of DILI ALF: Transplant-Free Survival versus Transplantation Plus Death

	Transplant-Free Survival		
Variable	**Yes (n = 36) (%)***	**No (n = 97) (%)***	***P***
Age (years)†	47.0 (30.5-54.5)	43.0 (34.0-55.0)	0.93†
Race‡			0.46‡
White	24 (31.6)	52 (68.4)	
Black	3 (14.3)	18 (85.7)	
Hispanic	5 (25.0)	15 (75.0)	
Other	4 (25.0)	12 (75.0)	
Gender			0.48
Male	12 (30.8)	27 (69.2)	
Female	24 (25.5)	70 (74.5)	
Drug class§			0.93
Antituberculosis	7 (28.0)	18 (72.0)	
Sulphur-containing	3 (27.3)	8 (72.7)	
Nitrofurantoin	3 (27.3)	8 (72.7)	
Antifungals	1 (20.0)	4 (80.0)	
CAMs, illicit drugs, etc.	3 (21.4)	11 (78.6)	
Antiepilepsy	5 (45.5)	6 (54.5)	
Antimetabolites	2 (18.2)	9 (81.8)	
Statins	3 (30.0)	7 (70.0)	
R value			0.26
Hepatocellular	26 (26.5)	72 (73.5)	
Mixed	2 (16.7)	10 (83.3)	
Cholestatic	7 (43.8)	9 (56.2)	
Discontinue time			0.10
Before onset of symptoms	7 (28.0)	18 (72.0)	
After onset of symptoms, before jaundice	9 (47.4)	10 (52.6)	
After onset of jaundice	20 (23.3)	66 (76.7)	
Coma grade			0.001
Grade 1	20 (47.6)	22 (52.4)	
Grade 2	10 (23.8)	32 (76.2)	
Grade 3	5 (18.5)	22 (81.5)	
Grade 4	1 (4.5)	21 (95.5)	
Interval (days)			
Onset to coma	12.0 (6.0-24.0)	16.0 (9.0-27.0)	0.26
Jaundice to coma	6.0 (0.0-14.0)	10.5 (5.0-21.0)	0.09
NAC			0.04
Yes	17 (38.6)	27 (61.4)	
No	19 (21.4)	70 (78.6)	
BMI	29.0 (25.1-34.4)	28.5 (24.3-32.5)	0.48
MAP	91.0 (76.0-96.5)	86.0 (77.0-95.0)	0.57
Bilirubin (mg/dL)	12.6 (5.2-24.1)	22.2 (16.3 -29.8)	<0.001
INR	2.0 (1.7-3.5)	2.9 (2.1-4.4)	0.007
Creatinine (mg/dL)	1.1 (0.8-3.1)	1.2 (0.8-2.8)	0.73
AST	588.5 (389.0-1418.5)	551.0 (267.0-1106.0)	0.26
ALT	784.5 (258.0-2013.5)	544.0 (253.0-1277.0)	0.28
Alkaline phosphatase	166.0 (130.0-239.0)	165.0 (118.0-220.0)	0.57
MELD score	29.0 (23.0-36.0)	34.0 (28.0-41.0)	0.006

Abbreviation: NAC, n-acetylcysteine.

* Number of subjects are also shown as percentage for each variable.

† Continuous variables analyzed by Wilcoxon rank sum test.

‡ Only selected drug classes (or individual drugs) taken by six subjects or more were included in the analysis.

§ Categorical variables analyzed by chi-square or Fisher's exact test.

and in U.S. ALF patients of any cause,[21,30,31] including DILI transplant recipients,[17] suggesting that women with acute liver injury are either more predisposed to develop ALF or use more prescription drugs than men.[32] Elsewhere, the representation of women compared to men among cases of nonacetaminophen DILI ALF is more variable.[16,18,30,33] Women are often, but not always, more susceptible than men to hepatotoxic drug reactions.[16,19,28,34–36]

Minorities were overrepresented, compared to the general U.S. population (U.S. Census, 2000[37]): white 57.1% versus 75.1%; African American 15.8% versus 12.3%; Hispanic 15.0% versus 12.5%; Asian 6.8% versus 3.6%; and Native American 2.3% versus 0.9%.

Racial/ethnic disparity occurs with both common[21] and rare[31] causes of ALF in the United States, but not among DILI cases that do not progress to ALF.[19] The DILI ALF racial/ethnic distribution seen here is atypical for acetaminophen-induced ALF in the United States (i.e., 88% white, 5% African American, 2% Asian, 2% Hispanic, and 1% Native American[26]). These gender and racial/ethnic variances should be explored further. That there are similar spontaneous survival rates among older compared to younger ALF subjects was shown earlier.[38] Not surprisingly, the elderly are selected less often for transplantation than the young.

Clinically, DILI can be distinguished from other causes of ALF by the drug history and subacute course. Typical allergic signature drug reactions were less frequent than suggested in a survey of common causes of DILI.[39] In the current study, significant titer autoantibodies (mostly ANA) were found in 24.1% of 79 subjects tested. Although some consider autoantibody positivity as evidence for an immunoallergic pathogenesis,[40] it is more likely a consequence and not a cause of liver damage, being found commonly in all-cause ALF.[41]

The assignment of DILI causality is difficult and circumstantial as there are no laboratory biomarkers yet for idiosyncratic hepatotoxins, as recently described for acetaminophen.[42] The many instruments devised for causality assignment are not entirely satisfactory,[43] and are especially difficult to apply in ALF, as data may be inaccurate when acquired urgently from encephalopathic sick patients and their distraught families. Thus causality was best determined here, as elsewhere,[19] by expert opinion. In the current study, the track record of the drugs and the rigorous clinical and laboratory exclusion of other hepatobiliary disorders were particularly useful. Only three cases were rejected as being indeterminate. The temporal relationship between ALF and drug use was not always clear cut, especially because drug discontinuation was unrelated to outcome, and spontaneous resolution was slow. In most cases, bad outcomes occurred before improvement was possible after drug discontinuation—so-called dechallenge. Rechallenge was rare. Concomitant drug use was extensive, including some drugs of high DILI potential. Few patients had signature presentations. For 20.3% of subjects exposed to only a single drug (or a limited drug combination) of high DILI potential, causality was easily recognized. Our causality assessment of DILI is likely to be as accurate as with any scoring system, for which most of the components required are not obtainable in ALF patients.

For practitioners seeing patients with unexplained acute liver disease, comprehensive catalogs of DILI ALF agents are useful, but these lists are only "snapshots" because prescribing practices vary geographically and temporarily.[3,24,34] Few biologicals were implicated here, but DILI from these compounds is emerging, including fatalities.[44] Within the broad spectrum of causative agents, antimicrobials dominate.[13,16,18,21] Isoniazid, as monotherapy or in combination, commonly causes hepatoxicity leading to liver transplantation,[17] followed by sulfur drugs, nitrofurantoin, other antibiotics, and antifungals. Amoxicillin-clavulanic and NSAIDs often cause DILI,[19,28,45] but less commonly ALF. Perhaps the inflammation caused by the infection for which antibiotics are prescribed, predisposes the patients to develop DILI.[46] Antiepileptics, antimetabolites, herbal mixtures and their derivatives, slimming potions, and illicit drugs, have strong reputations as hepatotoxins[7,47,48] and were well represented in our study. Statin prevalence ($n \geq 6$) was unexpected, as was the occasionally long duration of exposure (median 3-6 months; range, <1 month to 36 months; see also the footnote to Table 1C). Statin hepatotoxicity is generally benign,[49] but statins have been responsible for a few DILI-associated fatalities,[18,19] and atorvastatin-to-simvastatin substitution hepatitis has been reported.[50] In six subjects, a statin was the only potential DILI agent—albeit sometimes with a long latency (6-36 months in three of them)—and this increases confidence in our provocative observation that awaits confirmation by others. The latency between drug use and DILI onset varies, but is usually up to 3 months although delays of up to 12 months are considered compatible.[6,16,19,25,40,45] Extended latency is the norm for nitrofurantoin[51] and some other drugs, like diclofenac. In the current study, when the cause of DILI ALF was certain, the median exposure was 2 months, but even here six cases had 6 to 10 months of latency. For isoniazid median latency was 5 months; 6-8 months in one-third of the cases. As anticipated,[10,15,19,21] DILI in ALF was mostly hepatocellular (77.8%) compared to cholestatic and mixed reactions (19.2%) Conventional causes of cholestatic and mixed reactions (phenothiazines, macrolides, NSAIDs, carbamazepine, and phenytoin[34,52,53]) were rare. We confirmed that many drugs can cause cholestatic and mixed hepatotoxic reactions[16,19] (Table 3).

Three drugs in this study have been withdrawn (bromfenac and troglitazone because of hepatotoxicity, and cerivastatin because of rhabdomyolysis), and development of the hypoglycemic agent, TAK 559, was halted. Many drugs carry warnings of hepatotoxicity

(isoniazid, rifampin, ketaconazole, diclofenac, valproic acid, telithromycin, and interferon-β). All of the herbal, weight loss, and illicit substances or drugs are recognized hepatotoxins, and the FDA has recently warned against all usnic acid and Hydroxycut™ products.[24]

High mortality from idiosyncratic DILI ALF, has been observed.[21,30] In our study transplant-free survival was only 27.1% (Tables 4 and 5). Fortunately, 56 of the 73 listed remained eligible for liver transplantation, from which all but 4 (92.8%) survived, giving an overall survival of 66.2%. The 23.3% wait-list deaths attest to the urgent need for donor organs in this setting.[21] In multivariate analysis, coma grade, jaundice, coagulopathy, and MELD score all predicted transplant-free survival (Table 5). Most striking was the 43.2% lower bilirubin level (12.6 mg/dL) in transplant-free survivors, compared to those with severe outcomes (22.2 mg/dL; $P < 0.001$). Age,[16,18,30] duration of drug use,[19] ascites,[54] drug class,[16] and pattern of DILI reaction[16,18] were predictive of outcome in other studies but not here. Neither was the axiom upheld that cholestatic DILI is less life-threatening than hepatocellular DILI.[5]

BMI did not affect outcome in DILI ALF, as was seen in a larger study of all-cause ALF.[54] The trend to better outcomes when coma supervened soon after the onset of symptoms or jaundice has been observed elsewhere.[25,33] Intuitively, one would expect a good result if the offending drug were discontinued promptly when symptoms or liver test abnormalities occur, but that was not the case in our study, presumably because established ALF was the inclusion criterion. Although NAC use appeared to be associated with improved transplant-free survival (Table 5), the result of multivariable logistic regression analysis did not confirm NAC efficacy independent of MELD score and coma. It should be noted that the current study was not a randomized trial designed to test the effect of NAC on DILI ALF outcome, as reported elsewhere.[22]

In conclusion, DILI ALF disproportionately affects women and minorities and is most frequently caused by antimicrobials and to a lesser extent by antiepileptics, antimetabolites, statins, and herbal products. Presentations are subacute and though spontaneous survival is infrequent, for many patients liver transplantation is often feasible and highly successful. Survival in DILI ALF is determined by the degree of liver dysfunction. The selection bias of referral to highly specialized tertiary care centers, the imprecision of history in terms of duration of drug use, alcohol habit, and the effects of diabetes (which appear to reduce or facilitate DILI, respectively[19]), offer study opportunities that may permit future application of quantitative causality testing.

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