The Characteristics and Clinical Outcome of Drug-induced Liver Injury

A Single-center Experience

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Background and Goals: The aim of this cohort study was to determine the characteristics and clinical outcome of 170 patients with drug-induced liver injury (DILI) in a single center.

Study: Between January 2001 and June 2007, a total of 170 individuals who were diagnosed with DILI were retrospectively analyzed. The median follow-up period was 110.0 days.

Results: During the study period, a total of 5471 new patients were assessed for liver test abnormalities. Of those, 170 patients (3.1%) fulfilled the criteria of DILI. A total of 83 different drugs were considered to be related to the hepatotoxicity; a single drug was suspected in 57.6% of individuals. The median interval between the suspicious drug intake and DILI recognition was 15.0 days. Hepatocellular pattern was observed in 50.0% of patients with a mean alanine aminotransferase level of 952.2 ± 907.0 U/L. The main causative group of drugs was antibiotics. Sixty-two patients required hospitalization; acute liver failure developed in 14 (8.2%), chronicity was observed in 19 (11.2%), and 7 died (4.1%). Overall, complete recovery occurred in 82% of patients. The presence of jaundice on admission and shorter interval period between drug intake and DILI recognition were identified as risk factors for the development of acute liver failure.

Conclusions: DILI is an important cause of liver test abnormalities in outpatient clinics, and antibiotics represent the most common drug group. Overall, complete recovery after the withdrawal of the suspicious drug occurred in the majority of patients, but DILI may progress to acute liver failure, chronicity, and death.

Key Words: drug-induced liver injury, toxic hepatitis, hepatotoxicity, acute liver failure

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Drug-induced liver injury (DILI) is a serious common health problem in the general population.[1–5] Basically, each drug or its metabolite can cause hepatotoxicity. In the United States, DILI is responsible for approximately 13% of acute liver failure (ALF) and for approximately 0.1% to 3% of all hospital admissions annually.[6] The clinical presentation of DILI varies from asymptomatic liver test abnormalities to acute and chronic hepatitis.[7,8] It is usually a self-limiting disease, but may progress to ALF with a high mortality rate.[1–8]

The incidence of DILI in the general population remains unknown. According to reporting systems, the incidence rate of DILI in France and Spain was 14 and 34 cases per 100,000 individuals per year, respectively.[9,10] However, this number is likely underestimated because of the several limitations of the reporting systems. No DILI registry in Turkey exists at present. The aim of this cohort study was to determine the characteristics and clinical outcome of 170 patients diagnosed with DILI in a tertiary referral center in Turkey.

MATERIALS AND METHODS

Between January 2001 and June 2007, a total of 170 consecutive patients diagnosed with DILI who were seen at Ankara University Faculty of Medicine, Department of Gastroenterology, Liver Diseases Outpatient Clinic were retrospectively analyzed. The data were collected from outpatient visit charts. A history including the presence of medical illness, present and previous drug use, herbal remedies and mushroom intake, alcohol abuse, and drug addiction was obtained for all patients and family members if available. Criteria for inclusion were (1) age above 15 years; (2) absence of confounding disease including acute viral hepatitis (hepatitis A, B, C virus, cytomegalovirus, herpes simplex virus, and Epstein-Barr virus); (3) convincing evidence of absent or minimal alcohol consumption: < 15 g alcohol/day for women and < 20 g alcohol/day for men; (4) exclusion of other forms of liver disease including autoimmune, metabolic liver disease such as hemochromatosis, Wilson disease, α-1 antitrypsin deficiency, and biliary obstruction; (5) exclusion of alternative medicine (ie, herbal remedies, mushroom intake, and dietary supplements)-related hepatotoxicity; and (6) exclusion of severe heart and renal disease. Liver biopsies were available for histologic evaluation in 40 patients with DILI.

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Biochemical Tests

Serum alanine aminotransferase, aspartate aminotransferase, γ glutamyl transpeptidase, alkaline phosphatase, bilirubin, fasting glucose, cholesterol, and triglycerides levels and complete blood cell counts were measured by our central laboratory on a 24-channel automated chemical analyzer using standard reagents.

Serologic markers for viral infections (anti-hepatitis A virus IgM, IgG, HBsAg, anti-HBs, HBeAg, anti-HBe, anti-HBc IgM, IgG, anti-hepatitis C virus, anti-cytomegalovirus, anti-herpes simplex virus, and anti-Epstein-Barr virus) and serum iron, ferritin, copper, ceruloplasmin, and α-1 antitrypsin levels were measured, and serologic studies for anti-nuclear, anti-smooth muscle, anti-mitochondrial, and anti-LKM-1 antibodies were performed. Hepatitis B virus (HBV)-DNA and hepatitis C virus-RNA were analyzed using polymerase chain reaction in all patients for exclusion of other forms of liver disease. Abdominal sonography and nuclear magnetic resonance imaging were performed when a cholestatic pattern injury was present.

Definition

The diagnosis of DILI was based on the patient's history, clinical and biochemical characteristics, and histologic criteria, when available. The diagnosis was based on clinical suspicion, exclusion of other forms of liver disease, and consideration of the relationships between suspicious drug intake and onset of liver test abnormalities. Patients with underlying liver disease such as in inactive HBV carrier or nonalcoholic fatty liver disease (NAFLD) having normal liver tests were included into the study if they developed superimposed DILI. HBV-DNA levels in inactive HBV carriers with elevated liver enzymes were also checked using polymerase chain reaction to rule out HBV reactivation. The definition and pattern of DILI (hepatocellular, cholestatic, or mixed) were characterized based on the International Consensus Meeting criteria for liver injury.[11,12] Hepatocellular pattern of DILI was defined as the ratio (R) of serum alanine aminotransferase (as a multiple of its upper limit of normal) to serum alkaline phosphatase (as a multiple of its upper limit of normal) greater than 5, cholestatic as R less than 2, and mixed as R greater than 2 to less than 5.[11,12]

Follow-up

Patients who were not hospitalized were observed at regular intervals thereafter in the outpatient clinic, and the remaining hospitalized patients were regularly followed during the hospitalization period. Detailed history was taken, and vital signs and physical examination were assessed. Blood was drawn for determining biochemical parameters.

Patients with DILI were defined as resolved when abnormal liver tests had returned to normal within 3 months for hepatocellular pattern of injury or within 6 months for cholestatic or mixed pattern of injury. If no resolution was observed, patients were defined as chronic.[10]

Statistical Analyses

Data were analyzed with the Statistical Package for Social Sciences (SPSS version 11.0 SPSS Inc., Chicago, IL) for Windows software. Mann-Whitney U test and Kruskal-Wallis test were used for group comparisons and χ^2 and Fisher exact test for categorical variables. Mean ± SD and median (minimum to maximum) were given for continuous measurements. Frequencies and percentiles were given for categorical data. Multiple logistic regression was used to assess the risk factors. Variable selection in multiple logistic regression was carried out through backward elimination method. Odds ratios (ORs) and 95% confidence intervals (CIs) of ORs were given. Differences were reported as statistically significant if the P value was less than 0.05.

RESULTS

From January 2001 to June 2007, a total of 5471 new patients with liver test abnormalities were seen in our Liver Diseases Outpatient Clinic (670 cases in 2001, 701 in 2002, 765 in 2003, 880 in 2004, 901 in 2005, 952 in 2006, and 602 in the first 6 mo of 2007). Of those, a total of 170 patients (male/female: 75/95; mean age: 43.1 ± 14.4 y; range: 15 to 77 y) (3.1%) fulfilled the criteria of DILI; female sex was slightly predominant (55.8%); and 20 (11.8%) had known underlying liver disease with NAFLD and inactive HBV carrier status the most common diagnoses (7 and 6 patients, respectively), followed by others. One hundred and eight patients (63.5%) with or without diagnosed DILI were referred to our clinic as a tertiary center. The median follow-up period was 110 days (range: 3 to 1800 d).

A total of 83 different drugs were potential candidates for the hepatotoxicity. Hepatocellular pattern of liver injury was more commonly observed (85 of 170, 50%) followed by mixed pattern (44 of 170, 25.9%) and cholestatic pattern (41 of 170, 24.1%). The median duration of suspicious drug intake and median interval between suspicious drug intake and DILI recognition were 17.5 days (range: 1 to 2000 d) and 15 days (range: 1 to 150 d), respectively. These 2 periods were significantly shorter in individuals with hepatocellular pattern of injury as compared with the others ($P = 0.005$ and 0.001, respectively). Fatigue (61.8%), pruritus (31.8%), and jaundice (30%) were the most frequent symptoms during admission and these clinical presentations were more frequently associated with the hepatocellular pattern of injury ($P < 0.001$). No significant differences were observed between groups in terms of patient age, sex, and the presence of preexisting chronic liver disease ($P > 0.05$) (Table 1). The demographics and clinical and laboratory characteristics of the 170 patients with DILI are shown in Table 1.

A single drug was suspected as the cause of DILI in 98 individuals (57.6%), whereas more than 1 drug was suspected in the remaining 72 individuals. The main group of drugs associated with DILI was antibiotics (84 of 170, 49.4%), followed by nonsteroidal anti-inflammatory drugs (NSAID; 53of 170, 31.2%), antineoplastic agents (17of 170, 10.0%), and statins (14 of 170, 8.2%; Table 2). Amoxicillin-clavulanate was the most implicated antibiotic (31 of 84 patients, 36.9%), followed by metronidazole or ornidazole (19 of 84, 22.6%; Table 3).

In the histologic evaluation of liver biopsy specimens, cholestasis was more commonly reported in 42.5% of the DILI patients (17 patients): 13 of them had accompanying acute hepatitis and 2 had pure cholestasis. Acute hepatitis was reported in 10 patients (25%), chronic hepatitis in 6 (15%), steatohepatitis in 5 (12.5%), and reactive changes in 2.

Clinical Outcome

Sixty-two patients (36.5%, 62 of 170; 49 hepatocellular, 8 cholestatic, and 5 mixed) were hospitalized. ALF

TABLE 1. Characteristics and Clinical Outcome of Individuals With DILI Based on the Type of Liver Damage

	Whole Group (n = 170)	Hepatocellular (n = 85)	Cholestatic (n = 41)	Mixed (n = 44)	*P*
Mean age (y)	43.1 ± 14.4	41.44 ± 14.60	46.48 ± 13.05	43.00 ± 15.08	0.178*
Median (range)	44 (15-77)	43 (16-73)	48 (15-75)	42 (16-77)	
Female, n (%)	95 (55.8)	51 (53.7)	20 (48.8)	24 (54.5)	0.483†
Preexisting liver disease, n (%)	20 (11.8)	14 (16.5)	3 (7.3)	3 (6.8)	0.163†
Duration of drug intake (d) (median)	152.9 ± 405.8 (17.5)	68.6 ± 228.6 (15.0)	356.9 ± 626.6 (50.0)	125.7 ± 354.2 (15.0)	0.005*
Interval between drug intake and DILI recognition (d) (median)	22.9 ± 23.1 (15.0)	16.6 ± 13.6 (15.0)	34.7 ± 32.0 (30.0)	24.2 ± 24.2 (15.0)	< 0.001*
Clinical Presentation, n (%)					
Weakness	105 (61.8)	71 (67.6)	14 (34.1)	20 (45.5)	< 0.001†
Jaundice	51 (30)	40 (47.1)	7 (17.1)	4 (9.1)	< 0.001†
Pruritus	54 (31.8)	40 (47.1)	8 (19.5)	6 (13.6)	< 0.001†
Hospitalization	62 (36.5)	49 (57.6)	8 (19.5)	5 (11.4)	< 0.001†
Laboratory Parameters, mean value ± SD					
Serum alanine aminotransferase level (U/L)	534.3 ± 767.8	952.2 ± 907.0	70.0 ± 65.6	159.5 ± 110.7	< 0.001*
Median (range)	200 (16-5214)	673 (101-5214)	55 (16-417)	119.5 (53-534)	
Total bilirubin level (mg/dL)	5.6 ± 9.0	7.2 ± 9.5	4.3 ± 8.0	3.3 ± 8.0	0.002*
Median (range)	1.1 (0.1-36)	1.6 (0.1-35)	0.9 (0.1-30.6)	0.8 (0.1-36)	
Serum alkaline phosphatase level (U/L)	232.4 ± 228.0	221.7 ± 182.4	270.3 ± 333.9	217.7 ± 184.0	0.780*
Median (range)	159.5 (31-1878)	165.0 (31-805)	167.0 (52-1878)	152.0 (54-706)	
Clinical Outcome, mean value ± SD					
Follow-up (d)	215.0 ± 269.6	229.7 ± 257.4	264.3 ± 366.7	140.7 ± 150.9	0.112*
Median (range)	110 (3-1800)	150 (3-1440)	90 (30-1800)	90 (15-720)	
Duration of hospitalization (d) (n = 62)	19.2 ± 13.2	17.6 ± 12.4	26.8 ± 14.7	22.0 ± 16.8	0.124*
Median (range)	18 (1-60)	15 (1-45)	21(12-60)	18 (5-50)	
Recovery, mean (d) (n = 139)	53.1 ± 40.1	46.8 ± 23.5	69.7 ± 58.7	47.8 ± 37.2	0.380*
Median (range)	45 (7-180)	45 (15-90)	45 (10-180)	36 (7-180)	
Acute liver failure, n (%)	14 (8.2)	12 (14.1)	1 (2.4)	1 (2.3)	
Chronicity, n (%)	19 (11.2)	13 (15.3)	3 (7.3)	3 (6.8)	
Death, n (%)	7 (4.1)	6 (7.1)	1 (2.4)	0	

*Kruskal-Wallis test.
†Chi-square test were used.
DILI indicates drug-induced liver injury.

based on O'Grady criteria developed in 14 patients (14 of 170, 8.2%)[13]. Hepatocellular was the most common pattern of injury, and antibiotics and NSAID were the most frequently implicated drugs in patients who developed ALF (12 of 85, 14.1% vs. 1 of 41, 2.4% and 1 of 44, 2.3%). Among these 14 patients, 7 (6 hepatocellular pattern of injury) died in the hospital, 5 were liver-transplanted, and the remaining 2 patients (1 hepatocellular pattern of injury and 1 mixed pattern of injury) recovered. By multiple logistic regression analysis, the presence of jaundice on admission (OR: 16.44, 95% CI: 3.283-82.351) and the shorter interval between drug intake and DILI recognition (OR: 0.845, 95% CI: 0.748-0.955) were associated with the development of ALF (Table 4).

TABLE 2. The Main Drugs Suspected in 170 Individuals With Drug-induced Liver Injury

Drug	All Individuals (n)	Liver Injury Pattern		
		Hepatocellular	Cholestatic	Mixed
Antibiotics	84	49	13	22
Nonsteroidal anti-inflammatory drugs	53	25	7	21
Antineoplastic agents	17	8	5	4
Statins	14	10	4	0
Antipsychotics	12	3	8	1
Antituberculosis drugs	8	5	3	0
Antihypertensives	7	6	1	0
Antiepileptics	6	2	3	1
Antidiabetics	6	4	1	1
Myorelaxants	5	2	1	2
Antiulcer agents	4	4	0	0
Antifungals	4	1	0	3
Interferon	3	2	1	0

TABLE 3. Distribution of the Antibiotic Drugs

Drug Class	n	Type of Liver Injury		
		Hepatocellular	Cholestatic	Mixed
Penicillins (amoxicillin-clavulanate)	31	16	7	8
Metronidazole/ornidazole	19	13	0	6
Fluoroquinolones	11	6	3	2
Cephalosporins	9	6	0	3
Macrolide (clarithromycin)	8	3	3	2
Tetracycline	3	3	0	0
Sulfonamides/trimethoprim	3	2	0	1

TABLE 4. Factors Associated With the Development of Acute Liver Failure in Individuals With DILI

Factors	Odds Ratio	95% Confidence Interval	*P*
Univariate logistic regression analysis			
Age (y)	0.993	0.955-1.031	0.700
Gender (male/female)	2.088	0.628-6.944	0.230
Preexisting liver disease	1.803	0.223-14.753	0.580
Presence of jaundice on admission	18.00	3.858-83.979	< 0.001
Duration of drug intake (d)	0.999	0.998-1.001	0.570
Interval between drug intake and DILI recognition (d)	0.880	0.798-0.970	0.01
Serum alanine aminotransferase levels on admission (U/L)	1.001	1.000-1.001	0.001
Pattern of liver injury			
Hepatocellular vs. mixed	7.068	0.888-56.269	0.065
Cholestatic vs. mixed	1.075	0.065-17.767	0.960
Duration of hospitalization (d)	1.059	1.022-1.096	0.001
Multivariate logistic regression analysis			
Presence of jaundice on admission	16.44	3.283-82.351	0.001
Interval between drug intake and DILI recognition (d)	0.845	0.748-0.955	0.007

DILI indicates drug-induced liver injury.

Chronicity developed in 19 patients (11.2%) (male/female: 8/11; mean age: 44.7 ± 13.9 y). No significant relationship was found between any of the characteristics [age, sex, preexisting liver disease, duration of treatment (in days), interval between drug intake and DILI recognition (days), pattern of liver injury, and clinical and biochemical presentations during admission] and the development of chronicity ($P > 0.05$).

Recovery occurred in 39 hospitalized patients within a mean of 53.4 ± 36.1 days (median: 50 d, range: 7 to 180 d) and overall complete recovery occurred in 139 patients (139 of 170, 82%) within a mean of 53.1 ± 40.1 days (median: 45 d, range: 7 to 180 d) after discontinuation of the implicated drug (Table 1). Hospitalized patients were icteric as compared with nonhospitalized patients (mean serum total bilirubin levels: 12.3 mg/dL vs. 0.9 mg/dL, $P < 0.0001$, respectively). The pattern of liver injury did not affect recovery time ($P > 0.05$). Seven patients died in the hospital as a result of ALF leading to an overall mortality of 4.1%.

DISCUSSION

Establishing a diagnosis of DILI in an individual with elevated liver injury tests is often compelled because of the complete definition criteria of DILI. This cohort study retrospectively analyzed the characteristics and clinical outcome of DILI in a tertiary care center. DILI cases (basically moderate and severe DILI) and patients with elevated liver enzymes directly admitted or referred to this center for evaluation and management of their situation were included in this analysis. This represents a potential bias in patient selection. In fact, several investigators have mentioned the possibility of inaccurate diagnoses of DILI as reported in the Registry, because of the lack of international standards for its diagnosis, which is an important limitation of this reporting system.[10,14] In contrast, in this study, DILI diagnosis in each case was made on the basis of clinical assessment, biochemical parameters, and histologic evaluation when available, and we also ruled out other causes of liver injury. Thus, this analysis more clearly characterized the diagnosis of DILI and its clinical outcome in the long-term follow-up. Female sex showed slight predominance in this analysis. This is in line with some studies,[1,4] but conflicts with others.[10] Hepatocellular pattern of liver injury has been reported as the most commonly observed pattern in individuals with DILI, which was confirmed by this study (50% vs. 24% and 26%, respectively).

Hundreds of drugs available on the market have been implicated in hepatotoxicity. Antibiotics and NSAID are the most widely used medications worldwide. In this study, 83 different drugs were identified in 170 individuals with DILI. A single drug was implicated in approximately 58% of the individuals. In this analysis, antibiotics represented the main causative group and amoxicillin-clavulanate was the most frequently suspected drug, followed by NSAID, similar to results reported in earlier studies.[10,14,15] Several antibiotics have the potential to cause liver injury. The exact incidence of antibiotic-related liver injury is unknown. In 2 European studies, the incidence of antibiotic-related liver injury was estimated as approximately 1 to 3.5 patients/100,000 individuals/year.[9,10] Clinically, antibiotic-induced liver injury is mostly self-limited, but it may progress to ALF in some cases.[16] Antibiotic-induced liver injury represents all patterns of liver injury and 1 antibiotic may cause more than 1 pattern of injury.[16–19] Several reasons can explain antibiotics as the most implicated drug group related to hepatotoxicity, such as the high consumption of antibiotics in the general population, lax prescription policies concerning antibiotics in most countries including Turkey, and because infection and inflammation increase the susceptibility of the liver to some drugs, as suggested by several investigators.[20]

DILI, due to acetaminophen is the most common cause of ALF in Western countries and the United States,[6,21] whereas virus-induced ALF is the most common etiology in Turkey.[22] ALF developed in approximately 8% of individuals with DILI in this study, and hepatocellular pattern of injury was predominant. Earlier studies conducted in Spain and in the United States[10,14] were evaluated to identify the risk factors for the development of ALF in individuals with DILI. Female sex, pattern of liver injury, and serum bilirubin level on admission were identified as risk factors for the development of ALF in the Spain Cohort study,[10] but not in the US study.[14] In this study, on multivariate analysis, the presence of jaundice on

admission and shorter interval between drug intake and DILI recognition were associated with the development of ALF. However, the number of patients who developed ALF in this study is too small to strongly suggest the predictive factors for the development of ALF, which is the 1 limitation of the study.

In contrast, the finding of the presence of jaundice at presentation in DILI cases with hepatocellular pattern associated with the development of ALF, and subsequent mortality, is compatible with Hy rule that predicts the clinical outcome and prognosis of DILI with a high rate of mortality, from 10% to 50%.[8] Seven patients died during this study (4%) as a result of ALF. Six of them had hepatocellular pattern of injury with jaundice. The mortality was slightly lower and all of the mortality was liver-related in this study as compared with earlier studies.[10,14]

In this study, 12% of DILI individuals had preexisting liver disease. NAFLD and inactive HBV carrier status were the most common diagnoses identified. Preexisting liver disease in patients with DILI did not affect the development of ALF, chronicity, or the mortality in this study. Complete recovery after the implicated drug withdrawal is diagnostic for DILI and occurs in the majority of individuals with DILI. However, despite discontinuation of the implicated drug, chronicity may ensue in a small number of patients.[10,14,23,24] In this study, chronicity developed in 11% of the individuals, and overall complete recovery occurred in 139 patients (82%). The finding regarding the chronicity rate was compatible with earlier studies.[10,14] The present data showed that there was no predictable factor in individuals with DILI associated with the development of chronicity or mortality.

In conclusion, on the basis of the results of this study, DILI is one of the important causes of liver test abnormalities in outpatient clinics. Antibiotics, especially amoxicillin-clavulanate, represented the most common drug group related with hepatotoxicity. Overall, complete recovery after the withdrawal of the drug occurred in the majority of patients with DILI, but it may progress to ALF, chronicity, and death. The presence of jaundice on admission and shorter interval between drug intake and DILI recognition were identified as risk factors for the development of ALF.

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