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Clinical course and outcomes of drug-induced liver injury: Nimesulide as the first implicated medication

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ABSTRACT

Background and aims: Drug-induced liver injury (DILI) is the most common cause of death from acute liver failure, and accounts for approximately 13% of cases of acute liver failure in the United States. The clinical presentation of DILI covers a wide spectrum, from asymptomatic liver test abnormalities to symptomatic acute liver disease, prolonged jaundice and disability, or overt acute or subacute liver failure. The aim of our study was to evaluate the number of DILI cases admitted to our Unit and to identify the drugs responsible. Thus, we reviewed all clinical records of patients with DILI admitted to our Unit from 1996 to 2006.

Patients and methods: A database was constructed, reporting demographic, clinical features at onset, laboratory results, suspected drugs and follow-up. Liver damage was defined as hepatocellular, cholestatic or mixed, according to clinical and laboratory data.

Results: Forty-six patients were admitted with a diagnosis of DILI. Presentation was jaundice in 22 patients and hepatic failure in 3 (all attributed to nimesulide). Liver damage was of a cytolytic pattern in 19 cases (41%), cholestatic in 15 (33%) and mixed in 12 (26%). Jaundice was found to be higher in nimesulide-induced liver damage compared to other drugs ($p = 0.007$). Three out of 14 patients with nimesulide-induced DILI developed encephalopathy and/or ascites. Time of recovery in the nimesulide group was significantly lower than DILI from other drugs ($p < 0.001$).

Conclusion: Non-steroidal anti-inflammatory drugs, psychotropic drugs and antimicrobials are the most common causes of DILI. Nimesulide-induced DILI is usually reversible upon discontinuation of the drug, but occasionally progresses to liver failure.

1. Introduction

Drug-induced liver injury (DILI) is a health problem of increasing concern. Many currently used drugs, particularly non-steroidal anti-inflammatory drugs (NSAIDs), are implicated in liver disorders, ranging from mild aminotransferases elevation to fulminant hepatitis with a high rate of mortality [1]. While most subjects with clinically mild disease are diagnosed on an outpatient basis, patients with a more severe course require hospital admission and, in some cases, are evaluated for orthotopic liver transplantation (OLT).

A clinical picture resembling acute viral hepatitis with jaundice, malaise, anorexia, nausea and abdominal pain is the principal presentation of DILI, though other expressions of hepatotoxicity include chronic hepatitis, cirrhosis and the sinusoidal obstruction syndrome [2]. Liver histology can support the diagnosis through the finding of eosinophils, granulomas, microvescicular steatosis, or zonal hepatocellular necrosis. However, because a liver biopsy specimen is often not available, the pattern of drug-related liver injury is, from a practical point of view, classified according to laboratory data.

Classes of drugs most frequently involved in severe DILI seem to be antimicrobial and NSAIDs, followed by antidepressants, platelet aggregation inhibitors, statins and medicinal herbs [3–6]. Potential risk factors for DILI include a previous history of drug reactions, being very old or very young, female gender (especially for acute liver failure), multiple drug therapy, immunological disorders (HIV/AIDS, SLE), pre-existing liver disease, and poor nutritional status [7,8].

DILI is the leading reason for medications being withdrawn from the market in the United States, United Kingdom and Spain [9]. Spontaneous reporting is one of the surveillance systems routinely used to identify hepatic adverse drug reactions. This method, however, has often failed to quantify them in the general population. The numbers may be much higher, because of underreporting, difficulties in detection or diagnosis, and incomplete observation of

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exposed subjects. This was recently confirmed by a French prospective community study [10] in which incidence and seriousness of drug-induced hepatitis were largely underestimated in the general population.

Nimesulide is a relatively new NSAID, widely used in some European countries. Various reports of nimesulide hepatotoxicity [11,12] have been published, though how often this condition is reported is the subject of heated debate because spontaneous reports of adverse drug events are helpful warning signals, even if they do not allow clinicians to determine incidence or relative risk. Data obtained from population-based epidemiological studies reporting the incidence or comparative risks of hospitalisation and death are, in fact, lacking.

In our study we aimed to evaluate retrospectively the rate of severe cases of DILI admitted to our Unit, a tertiary referral centre for liver disease, over a 10-year period, and to identify the drugs most commonly responsible.

2. Patients and methods

We retrospectively reviewed all clinical records of patients admitted to our Unit, which is a tertiary referral centre for chronic liver disease, from January 1996 to December 2006. Among a total of 6123 clinical charts of patients admitted, 5787 had a discharge diagnosis, and 336 were not defined because clinical records were missing, or the patients were undiagnosed or were drop-outs from outpatient visits (Fig. 1).

Among patients with a well-defined discharge diagnosis, outcomes were assessed by clinical, laboratory and imaging tests, together with liver histology, when available. Cases of hepatocellular patterns of damage were defined as chronic if liver tests showed a persistent abnormality more than 3 months after stopping drug therapy. In the case of cholestatic/mixed type of injury, the abnormality needed to be persistent for more than 6 months following drug withdrawal. Cases were defined as resolved when liver test values returned within laboratory reference ranges within this time period.

For all patients, a detailed history was obtained concerning antecedents of liver or biliary disease, drug addiction and/or alcohol abuse, transfusion of blood products, or surgery within 6 months preceding the onset of liver disease. A computerised database was constructed, reporting data regarding age, gender, clinical features at onset, laboratory results, suspected drugs and follow-up. All patients were tested for hepatitis A, B, C, EBV and CMV serology. In addition, autoantibody screening was done. Excluded from the present analysis were cases of hepatic damage that were secondary to occupational exposure to toxins. By contrast, we included in our study patients with underlying liver disease by aiming to evaluate whether drug-mediated liver damage might worsen the prognosis. Only cases considered as being drug-related according to the clinical judgment of experts were then assessed using the Council for International Organizations of Medical Sciences (CIOMS) scale [9], and only when the cases were classified as definite, highly probable, probable, or possible, were the data incorporated into the database.

The pattern of liver injury and the chronological relationship between drug assumption and onset of hepatitis were defined according to International Consensus Criteria [13,14]. Liver damage was defined as an increase of alanine aminotranferase (ALT) or conjugated bilirubin 2 times normal range or combined increase in aspartate aminotransferase (AST), alkaline phosphatase (AP), and total bilirubin, provided that one of them was twice above normal. "Cytolytic" type was defined as an ALT/AP ratio of >5, "cholestatic" type as a ratio of <2, and "mixed" as a ratio between 2 and 5 [13–15]. The liver tests used for the classification of liver damage were the first blood test available at the time liver injury was suspected.

Cases were considered immunoallergic if they presented with any of the classical clinical or laboratory features of allergy (fever, rash, serum eosinophilia, cytopenia, or detectable titers of autoantibodies) and/or if they were accompanied by histopathologic findings (eosinophil-rich inflammatory infiltrate and/or granuloma formation). In the remaining cases, the mechanism was presumed to be metabolic idiosyncrasy.

On the basis of the type of drug involved in the adverse reaction, we identified four groups, divided as follows: patients with NSAID (nimesulide, ibuprofen, mesalazine) drug adverse reaction; patients with antimicrobial (amoxicillin–clavulanate, tazobactam, albendazole) adverse reactions; patients with psychotropic (oxcarbamazepine, haloperidol, lithium and carbolithium, lorazepam, fenobarbital) adverse reactions; and patients with adverse reactions to statins (simvastatin, fluvastatin), to oral hypoglycaemic agents (gliclazide, glimepiride), and anti-platelets (aspirin, ticlopidine, clopidogrel). A single prescription medication was implicated

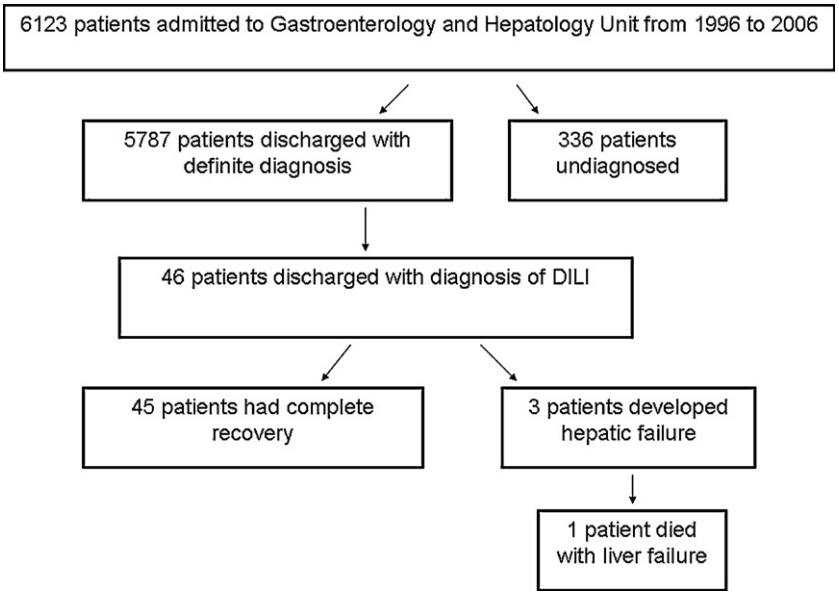

Fig. 1. Flow-diagram of patients admitted to Gastroenterology and Hepatology Unit from 1996 to 2006.

Table 1
Demographic, clinical and laboratory characteristic of 46 patients with drug-induced liver injury.

Variable	
Age (years)[a]	54(43–67)
Gender	
Male	23(50.0%)
Female	23(50.0%)
BMI[a]	25(22.0–28.0)
Previous chronic liver disease	5(10.9%)
Drugs	
NSAIDs and paracetamol	20(43.5%)
Psychotropic	6(13.1%)
Antimicrobial	5(10.8%)
Others	15(32.6%)
Jaundice at diagnosis	22(47.8%)
ALT (UI/l)[a]	340(155–892)
ALP (UI/l)[a]	280(210–438)
γGT (UI/l)[a]	150(70–465)
Bilirubin (mg/dl)[a]	3.0 (1.0–12.75)
INR[a]	1.0 (1.0–1.1)
WBC[a]	6675.0 (5320.0–8805.0)
Eosinophil (%)[a]	2(0.6–3.0)
Creatinin[a]	0.95 (0.6–1.2)
Type of liver damage	
Cytolitic	19(41.3%)
Cholestatic	15(32.6%)
Mixed	12(26.1%)
Time to recovery (weeks)[a]	8(5–8)

NSAIDs: non-steroidal anti-inflammatory drugs; ALT: alanine aminotransferase; ALP: alkaline phosphatase; γGT: gamma-glutamyltransferase; INR: international normalized ratio; WBC: white blood cells.
[a] Median, interquartile range (IQR).

in 36 (78%) of the 46 patients; while in 10 (22%) patients, more than one prescription medication was implicated. A complete list of agents implicated is provided in supplementary Table 1.

All patients had regular follow-up visits every 3 months for at least 1 year after discharge. All of them were contacted by phone in January 2007 in order to update clinical outcomes.

Data were analysed with SPSS version 13.0 for Windows. Variables were examined using descriptive statistics. Bivariate associations were measured using the Mann–Whitney and Kruskall–Wallis tests for continuous variables, and the chi-square test for categorical items. ANOVA was used for comparisons of groups. Differences were reported as statistically significant if the *P* value was less than 0.05.

3. Results

Demographic, clinical and laboratory features of patients with DILI are shown in Table 1. Forty-six of the 6123 patients admitted to our Unit in the above-mentioned period received a discharge diagnosis of DILI. There were 23 men and 23 women, the mean age was 54, ranging from 11 to 88 years, and 36 patients (78%) were above the age of 40. Five of these 46 patients had an underlying liver disease: 3 were HCV-related chronic liver disease (2 hepatitis and 1 cirrhosis); 1 had cryptogenic cirrhosis, and 1 had a dual HBV/HCV chronic infection with persistently normal ALT. Presentation was jaundice in 22 patients. Three patients developed hepatic failure, manifested by hepatic encephalopathy and ascites. Type of damage was cytolytic in 19 cases, cholestatic in 15, and mixed in 12 cases. Median value of ALT among all cases was 360 UI/l. Median value of ALP was 280 UI/l. Median value of γGT was 400 UI/l.

In our study, the association between alcohol consumption and susceptibility to DILI was evaluated. Alcohol abuse was defined as an alcohol intake of ≥30 ml/day in males and of ≥20 ml/day in females in the preceding 12 months. None of the enrolled patients had a history of alcohol abuse. Liver steatosis was found on ultrasound in 10 patients regardless of the class of drug; 7 patients out of 10 were affected with metabolic syndrome.

Anti-inflammatory agents were responsible for the injury in 20 cases, of which 17 attributed to NSAIDs and 3 to paracetamol. Among the 17 cases related to NSAIDs, 14 were attributed to nimesulide. Psychotropic drugs were involved in 6 cases, and antimicrobials in 5 cases. Other drugs most frequently involved in liver damage, either by themselves or in association with other drugs, were anti-platelets, anti-diabetic drugs and statins; the remaining 15 cases of liver damage were included in this group.

Liver biopsies were performed in 15 of the 46 patients. Six patients in the NSAIDs group had a liver biopsy, and all of them had been previously treated with nimesulide. Four patients received psychotropic drugs, and the remaining 5 cases were treated with miscellanea of drugs. Histopathologic features of biopsy specimens are shown in Table 2.

We verified whether demographic, clinical and laboratory features of patients were significantly different among the three types of liver damage, and found no significant differences in age, gender, presence of jaundice, type of drug, outcome and time of follow-up. The median value of ALT was significantly higher in cytolitic damage than in mixed or cholestatic ones (880 IU/l vs. 320 IU/l vs. 140 IU/l; $p < 0.001$), median values of ALP and γGT were significantly higher in cholestatic damage than in mixed or cytolitic ones (ALP: 560 IU/l vs. 322 IU/l vs. 280 IU/l; $p < 0.001$) (γGT: 325 IU/l vs. 100 IU/l vs. 150 IU/l; $p < 0.042$) (Table 2). NSAIDs were involved in all cases of hepatic failure. In this group, 14 patients (70%) had liver damage attributed to nimesulide. Seven were men and 7 women; mean age was 58. Only 1 patient had pre-existing chronic HBV/HCV infection with persistently normal ALT. Eleven out of 14 patients presented with jaundice; the prevalence of jaundiced patients in this group was significantly higher than in other patients (78.6% vs. 34.4%; $p = 0.013$). All patients in this group had a median ALT value of 700 IU/l, ranging from 120 to 2400 IU/l; 3 out of 11 patients developed severe hepatic failure with encephalopathy and/or ascites. Eight patients had a cytolytic liver damage, 3 cholestatic and 3 mixed. By statistical analysis, the median ALT value was significant higher in these patients compared with the other group of drugs, NSAIDs included (700 ULN vs. 300 ULN; $p < 0.001$). Liver biopsies performed in 6 patients showed centrilobular or panlobular bridging necrosis with mild intrahepatic cholestasis. One patient with liver failure died while on the waiting list for liver transplant. Another patient developed autoimmune hepatitis with ANA positivity. In all other patients, liver tests returned to normal values within the follow-up period. Recovery time in the nimesulide group was significantly shorter compared to other patients (4 weeks vs. 8 weeks; $p < 0.001$) (Table 3). All patients had a complete recovery, with normal LFT, at the end of follow-up. Most patients with nimesulide-adverse reaction were administered one single dose of medication.

4. Discussion

The potential hepatotoxicity of common therapeutic drugs, along with herbal remedies, is widely recognised as a major challenge in contemporary hepatology. In this study, we retrospectively analysed records of 46 patients with severe clinical course. A cytolytic pattern of liver damage was found in 19 cases, a cholestatic pattern was found in 15 cases, and a mixed pattern in the remaining cases. The class of drugs most responsible was NSAIDs, in which 14 cases were attributable to nimesulide. In the cytolitic pattern, the mean value of aminotransferases was significantly higher than in the mixed or cholestatic pattern ($p < 0.001$), and in the cholestatic

Table 2
Demographic, clinical and laboratory features of 46 patients with drug-induced liver injury according to type of hepatic damage.

Variable	Cytolytic [19]	Cholestatic [15]	Mixed [12]	*P*
Age (years)[a]	55 (36–68)	58 (47–74)	49.5 (38–66)	n.s.
Gender				
Male	8 (42%)	9 (60%)	6 (50%)	n.s.
Female	11 (58%)	6 (40%)	6 (50%)	
BMI[a]	28.4 (27.3–29.4)	25 (24–28)	20.2 (18.3–22)	n.s.
Drugs				
NSAIDs and paracetamol	10 (53%)	6 (40%)	4 (33%)	n.s.
Psychotropic	2 (16%)	0	2 (17%)	
Antimicrobial	3 (10%)	2 (13%)	2 (17%)	
Others	4 (21%)	7 (47%)	4 (33%)	
Jaundice at diagnosis	8 (42%)	8 (53%)	6 (50%)	n.s.
Hepatic failure	1 (5.3%)	1 (6.7%)	1(8.3%)	n.s.
ALT (UI/l)[a]	880 (520–1800)	140 (60–320)	300 (130–350)	<0.001
ALP (UI/l)[a]	280 (140–350)	560 (280–1680)	315 (228–473)	0.002
γGT (UI/l)[a]	150 (75–275)	325 (95–800)	100 (50–400)	n.s.
Bilirubin (mg/dl)[a]	1 (1–11)	8.2 (1–23.2)	5.4 (1–12.5)	n.s.
INR[a]	1 (1–1.45)	1.1 (1–1.1)	1 (1–1.1)	n.s.
WBC (mm^3)[a]	5350 (5190–10,150)	7000 (3750–8745)	7020 (6215–10,860)	n.s.
Eosinophil (%)[a]	2.1 (0.3–2.6)	2.3 (0.2–4.9)	2.0 (1.7–3.9)	n.s.
Creatinin[a]	1 (0.7–1.2)	1.20 (6–1.4)	0.7 (0.6–0.9)	n.s.
Histological features[b]	(5 patients)	(6 patients)	(4 patients)	n.s.
Necroinflammation	5	6	4	
Cholestasis	3	6	1	
Lipofuscin	0	0	2	
Granulomatosis	1	0	0	
Steatosis	1	0	0	
Time to recovery (weeks)[a]	5.5 (4–8)	8 (7–8)	7.5 (5–8)	n.s.

NSAIDs: non-steroidal anti-inflammatory drugs; ALT: alanine aminotransferase; ALP: alkaline phosphatase; γGT: gamma-glutamyltransferase; INR: international normalized ratio; WBC: white blood cells.
[a] Median, IQR.
[b] Fifteen patients with liver biopsy.

pattern, the mean values of ALP and γGT were higher than in the mixed and cytolytic patterns ($p < 0.001$ and $p < 0.042$, respectively). Further, it is worth noting that 5 patients with pre-existing chronic liver disease completely recovered from the liver damage, and none progressed to chronicity. Among the 14 cases with adverse reaction to nimesulide, the prevalence of patients with jaundice at onset was significantly higher compared to all other drugs. In the nimesulide group only, three patients progressed to subacute hepatic failure, again a significant difference compared with all other hepatotoxins. An important finding of our study was that more than one agent was implicated in causing liver injury in 22% of cases, the same frequency reported by Chalasani [16]. In contrast, in our

Table 3
Demographic, clinical and laboratory differences among patients with drug-induced liver injury from nimesulide or other drugs.

	Nimesulide [14]	Other drugs [32]	*P* value
Age (years)[a]	60 (50.8–66.2)	52 (36–71)	n.s.
Gender			
Male	7 (50%)	16 (50%)	n.s.
Female	7 (50%)	16 (50%)	
BMI[a]	27.3 (24–29.4)	23.5 (19.2–27.2)	n.s.
Jaundice at diagnosis	11 (78.6%)	11 (34.4%)	0.007
Hepatic failure	3 (21.4%)	0	0.006
ALT (UI/l)[a]	700 (320–1850)	300 (120–750)	0.007
ALP (UI/l)[a]	315 (210–648)	280 (210–420)	n.s.
γGT (UI/l)[a]	350 (113–425)	150 (50–500)	n.s.
Bilirubin (mg/dl)[a]	12.8 (2.9–22.8)	1.1 (1.0–8.2)	0.013
INR[a]	1.1 (1.0–1.6)	1.0 (1.0–1.1)	n.s.
WBC (mm^3)[a]	7200 (4750–22,420)	6550 (5330–8660)	n.s.
Eosinophil (%)[a]	2.3 (0.1–2.9)	2.0 (0.8–3.1)	n.s.
Creatinin[a]	0.7 (0.6–1.3)	1 (0.6–1.2)	n.s.
Type of liver damage			
Cytolitic	8 (57.2%)	11 (34.4%)	n.s.
Cholestatic	3 (21.4%)	12 (37.5%)	
Mixed	3 (21.4%)	9 (28.1%)	
Time to recovery (weeks)[a]	4 (4–6)	8 (7–8)	<0.001

NSAIDs: non-steroidal anti-inflammatory drugs; ALT: alanine aminotransferase; ALP: alkaline phosphatase; γGT: gamma-glutamyltransferase; INR: international normalized ratio; WBC: white blood cells.
[a] Median, IQR.

study we reported no DILI caused by dietary supplements or herbal medications, because in Italy their use is very uncommon.

Drugs most frequently recorded as the cause of liver damage in our cohort were similar to those found in recent studies [3–6,16]. NSAIDs, psychotropic and antimicrobial agents were those most commonly involved, followed by anti-platelets, anti-diabetic drugs, and statins. According to an international panel, acute liver injuries can be classified into three groups, using biochemical criteria based on ALT, AP and their ratio [12]. This classification has the advantage of separating hepatitis type with different courses and prognostic features. The predominant pattern of hepatic damage was cytolytic, as has consistently been demonstrated in other, larger, case series [5,6,13]. The most common drugs correlated with cytolytic damage are antibiotics and NSAIDs; psychotropic drugs are mainly implicated in mixed damage. Azathioprine, anti-platelets, anti-diabetic drugs and statins are correlated with cholestatic damage.

Our definition of chronic DILI follows the International Criteria [12], which defines chronic liver injury as abnormal liver tests for a period of more than 3 months. Other investigators have suggested that this period should be 6 months [17]. Evidence from several case reports [18–20], and general consensus, suggest that cholestatic/mixed lesions subside more slowly than cytolytic injury. We analysed the two types separately, and indeed the dechallenge scoring of the CIOMS scale showed a different time scale according to the type of damage (1 month for hepatocellular injury, and up to 6 months for the cholestatic/mixed type damage), with a range of variability of 2–48 months.

In our study, among the 5 cases of hepatotoxicity related to antimicrobials, 4 were due to amoxicillin/clavulanate, which is the most frequent class of agents associated with DILI [5,10,21]. The overall rate of symptomatic hepatitis due to amoxicillin–clavulanic acid is estimated at less than 1 in 100,000 [22] and the pattern of hepatotoxicity is a cholestatic reaction that develops 1–4 weeks after cessation of therapy [22–25]. However, delayed onset of symptoms can be seen up to 8 weeks following discontinuation of therapy [22,25], and prolonged cholestasis with ductopenia following cessation of therapy has also been described [26]. In our study we found that the liver damage due to amoxicillin–clavulanate was cytolytic in two cases, cholestatic in one and mixed in the other one. Mean follow-up of these cases was about 40 months, with complete recovery.

Jaundice is most common in liver injury caused by NSAIDs, and further jaundice associated with ALT elevation portends a worse prognosis compared with aminotransferase elevation alone [27,28]. In our study, in the NSAIDs group we found that 14 patients (70%) had liver damage attributable to nimesulide. This is a drug with potent anti-inflammatory, analgesic and antipyretic characteristics, and widely used in clinical practice. Adults, elderly and paediatric patients tolerate it well, and its pharmacodynamic profile would seem to suggest fewer gastrointestinal problems. The number of patients with elevated aminotransferases during treatment with nimesulide is, however, increasing, and cases of fulminant and subacute hepatitis, sometimes fatal, have been documented. Two different pathological patterns of nimesulide-induced DILI (i.e. hepatocellular necrosis and pure cholestasis) have been documented, and could be related to the gender of the patient. In our case series, 50% were women, with a higher frequency of cytolitic and a lower frequency of cholestatic patterns than males. Advanced age may affect the likelihood of adverse hepatic reactions to the drug in general [29]. In fact, the majority of our nimesulide cases were above the age of 40. In the nimesulide group, the patients had the highest mean values of aminotransferases, though they also had the shortest recovery time. To further stress that nimesulide-induced DILI may have a severe outcome, the only 3 patients with hepatic failure, encephalopathy and ascites due to DILI belonged to the nimesulide group. One of them died while on waiting list for OLT.

An interesting finding is the association between increased BMI and steatosis in the patients with DILI caused by NSAIDs. In our study, 10 patients with cytolytic liver damage caused by NSAIDs had a mean BMI of 28. However, liver steatosis detected on ultrasound was also reported in 10 patients with DILI caused not only by NSAIDs, but by other drugs as well. Seven of these patients were also affected by metabolic syndrome.

Approximately 7% of patients in our series showed features of hypersensitivity, including rash, urticaria and pruritus, with no sign of hypereosinophilia on cell blood count. Interestingly, in a large cohort of patients with drug-induced idiosyncratic liver disease [30], a link between HLA class II and cholestatic/mixed injury was reported. This would suggest that the majority of cholestatic/mixed injury cases may have a genetically based allergy component. This is less certain in cytolytic injury cases with hypersensitivity features [31].

All our cases during follow-up showed a complete recovery from DILI, including the 5 patients with pre-existing liver disease. This is probably linked to the prompt withdrawal of the culprit drug after an adverse reaction was suspected. In fact, continuing therapy with a hepatotoxic drug that causes jaundice could be, as suggested by Zimmerman [2], an important risk factor for the development of liver failure. Rapid cessation of the incriminated drug in a case of suspected DILI could be of major importance [21]. Thus, prompt recognition of drugs causing hepatotoxicity and cessation of these drugs is not only important for decreasing the risk for acute liver injury, but also for avoiding chronic consequences of DILI [32].

In conclusion, DILI is a persistent and challenging problem for physicians, health agencies and pharmaceutical firms. To date, most clues indicate that idiosyncratic hepatotoxicity results from a combination of genetic and environmental factors. Elucidation of these factors should leads to clinical tests that can identify susceptible patients, so that the toxicity can be detected early on, prevented, and, finally, accurately treated.

Conflict of interest statement
None declared.

List of abbreviations

ADR, adverse drug reaction; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; NAFLD, non-alcoholic fatty liver disease; NSAIDs, non-steroidal anti-inflammatory drugs; OLT, orthotopic liver transplantation; SLE, serum lupus erythematosus; ULN, upper limit of normal.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.dld.2009.06.009.

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