Research Article

JOURNAL OF HEPATOLOGY

Definition and risk factors for chronicity following acute idiosyncratic drug-induced liver injury

Inmaculada Medina-Caliz[1,a,†], Mercedes Robles-Diaz[1,a,†], Beatriz Garcia-Muñoz[1], Camilla Stephens[1,a], Aida Ortega-Alonso[1], Miren Garcia-Cortes[1,a], Andres González-Jimenez[1], Judith A. Sanabria-Cabrera[1], Inmaculada Moreno[1,a], M. Carmen Fernandez[2], Manuel Romero-Gomez[3,a], Jose M. Navarro[4], Ana Mª Barriocanal[5], Eva Montane[5], Hacibe Hallal[6], Sonia Blanco[7], German Soriano[8,a], Eva M. Roman[8,a], Elena Gómez-Dominguez[9], Agustin Castiella[10], Eva M. Zapata[10], Miguel Jimenez-Perez[11], Jose M. Moreno[12], Ana Aldea-Perona[13], Manuel Hernández-Guerra[14], Martin Prieto[15,a], Miguel E. Zoubek[1], Neil Kaplowitz[16], M. Isabel Lucena[1,a,*], Raul J. Andrade[1,a], on behalf of the Spanish DILI registry

[1]*Unidad de Gestión Clínica de Aparato Digestivo, Servicio de Farmacología Clínica, Instituto de Investigación Biomédica de Málaga-IBIMA, Hospital Universitario Virgen de la Victoria, Universidad de Málaga, Málaga, Spain;* [a]*Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Spain;* [2]*Servicio de Farmacia, Hospital de Torrecárdenas, Almería, Spain;* [3]*UCM Digestive Diseases, Virgen del Rocio University Hospital, Sevilla, Spain;* [4]*Area Integrada de Gestión de Medicina Interna, Hospital Costa del Sol, Marbella, Málaga, Spain;* [5]*Servicio de Farmacología Clínica, Hospital Germans Trias i Pujol, Badalona, Barcelona, Spain;* [6]*Servicio de Digestivo, Hospital Morales Meseguer, Murcia, Spain;* [7]*Servicio de Aparato Digestivo, Hospital de Basurto, Bilbao, Vizcaya, Spain;* [8]*Servicio de Patología Digestiva, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain;* [9]*Servicio de Aparato Digestivo, Hospital Universitario 12 de Octubre, Madrid, Spain;* [10]*Servicio de Digestivo, Hospital de Mendaro, Guipúzcoa, Spain;* [11]*Unidad de Gestión Clínica de Aparato Digestivo, Instituto de Investigación Biomédica de Málaga-IBIMA, Hospital Universitario Regional de Málaga, Málaga, Spain;* [12]*Servicio de Digestivo, Complejo Hospitalario Universitario de Albacete, Albacete, Spain;* [13]*Servicio de Farmacología Clínica, Hospital Universitario de Canarias, La Laguna, Tenerife, Spain;* [14]*Servicio de Digestivo, Hospital Universitario de Canarias, La Laguna, Tenerife, Spain;* [15]*Unidad de Hepatología, Hospital La Fe, Valencia, Spain;* [16]*USC Research Center for Liver Diseases, Keck School of Medicine, Los Angeles, CA, United States*

Background & Aims: Chronic outcome following acute idiosyncratic drug-induced liver injury (DILI) is not yet defined. This prospective, long-term follow-up study aimed to analyze time to liver enzyme resolutions to establish the best definition and risk factors of DILI chronicity.

Methods: 298 out of 850 patients in the Spanish DILI registry with no pre-existing disease affecting the liver and follow-up to resolution or ⩾1 year were analyzed. Chronicity was defined as abnormal liver biochemistry, imaging test or histology one year after DILI recognition.

Results: Out of 298 patients enrolled 273 (92%) resolved ⩽1 year from DILI recognition and 25 patients (8%) were chronic. Independent risk factors for chronicity were older age [OR: 1.06, $p = 0.011$], dyslipidemia [OR: 4.26, $p = 0.04$] and severe DILI [OR: 14.22, $p = 0.005$]. Alanine aminotransferase (ALT), alkaline phosphatase (ALP) and total bilirubin (TB) median values were higher in the chronic group during follow-up. Values of ALP and TB >1.1 x upper limit of normal (xULN) and 2.8 xULN respectively, in the second month from DILI onset, were found to predict chronic DILI (p <0.001). Main drug classes involved in chronicity were statins (24%) and anti-infectives (24%). Histological examination in chronic patients demonstrated two cases with ductal lesion and seven with cirrhosis.

Conclusions: One year is the best cut-off point to define chronic DILI or prolonged recovery, with risk factors being older age, dyslipidemia and severity of the acute episode. Statins are distinctly related to chronicity. ALP and TB values in the second month could help predict chronicity or very prolonged recovery.

Lay summary: Drug-induced liver injury (DILI) patients who do not resolve their liver damage during the first year should be considered chronic DILI patients. Risk factors for DILI chronicity are older age, dyslipidemia and severity of the acute episode. Chronic DILI is not a very common condition; normally featuring mild liver profile abnormalities and not being an important clinical problem, with the exception of a small number of cases of early onset cirrhosis.

Keywords: Hepatotoxicity; Chronic; Risk factors; Statins.

Received 1 December 2015; received in revised form 5 May 2016; accepted 9 May 2016; available online 13 May 2016

* Corresponding author. Address: Servicio de Farmacología Clínica, Instituto de Investigación Biomédica de Málaga-IBIMA, Hospital Universitario Virgen de la Victoria, Facultad de Medicina, Universidad de Málaga, Boulevard Louis Pasteur, 32 29071 Málaga, Spain. Tel.: +34 952 131572; fax: +34 952 131568.

E-mail address: lucena@uma.es (M.I. Lucena).

† These authors contributed equally to this work.

Abbreviations: DILI, drug-induced liver injury; ALP, alkaline phosphatase; TB, total bilirubin; ULN, upper limit of normal; AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio; R, ratio; HC, hepatocellular; Chol, cholestatic; Mix, mixed; CIOMS, Council for International Organizations of Medical Sciences; RUCAM, Roussel Uclaf causality assessment method; NASH, non-alcoholic steatohepatitis.

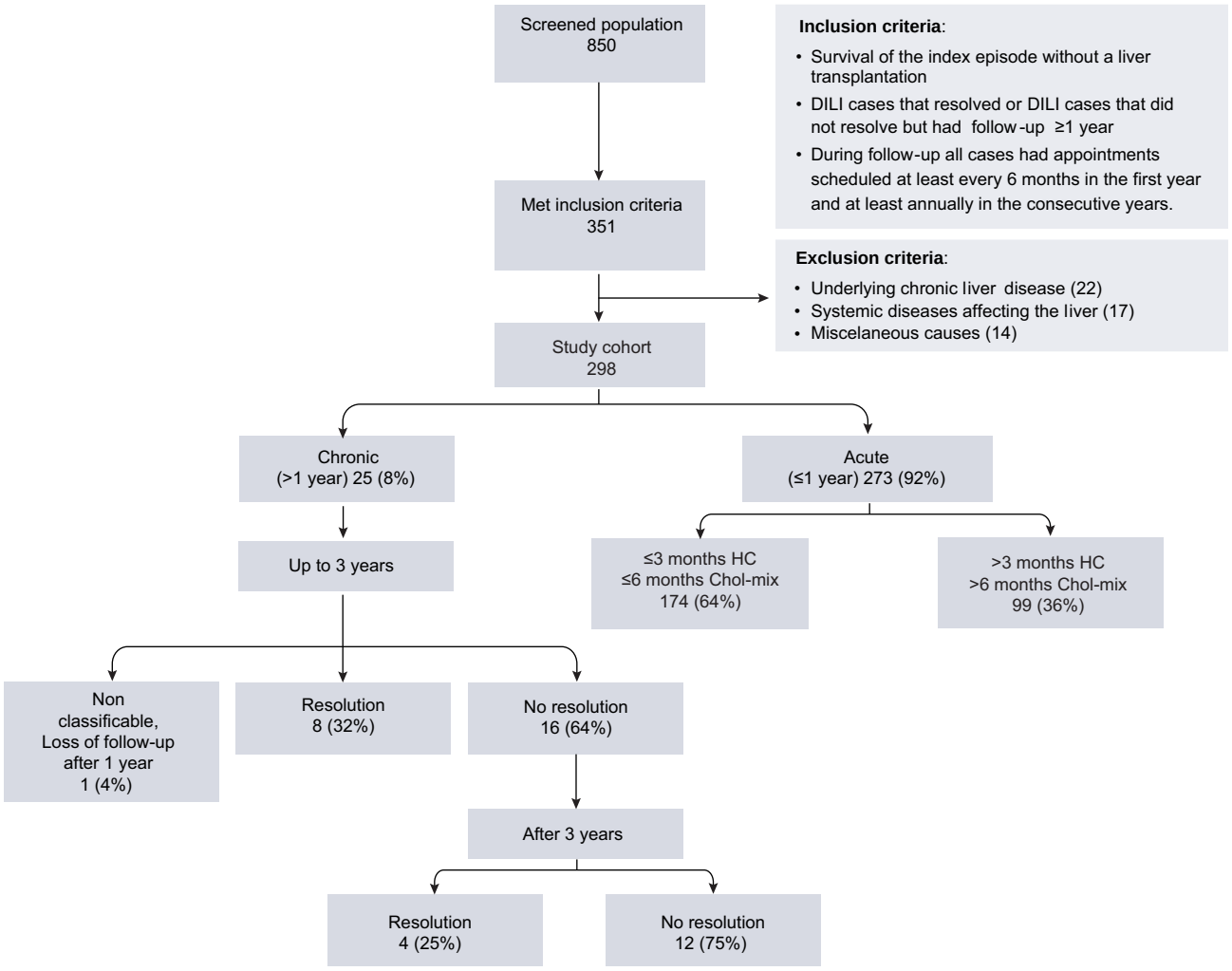


Fig. 1. Flow chart of the study cohort.

© 2016 European Association for the Study of the Liver. Published by Elsevier B.V. All rights reserved.

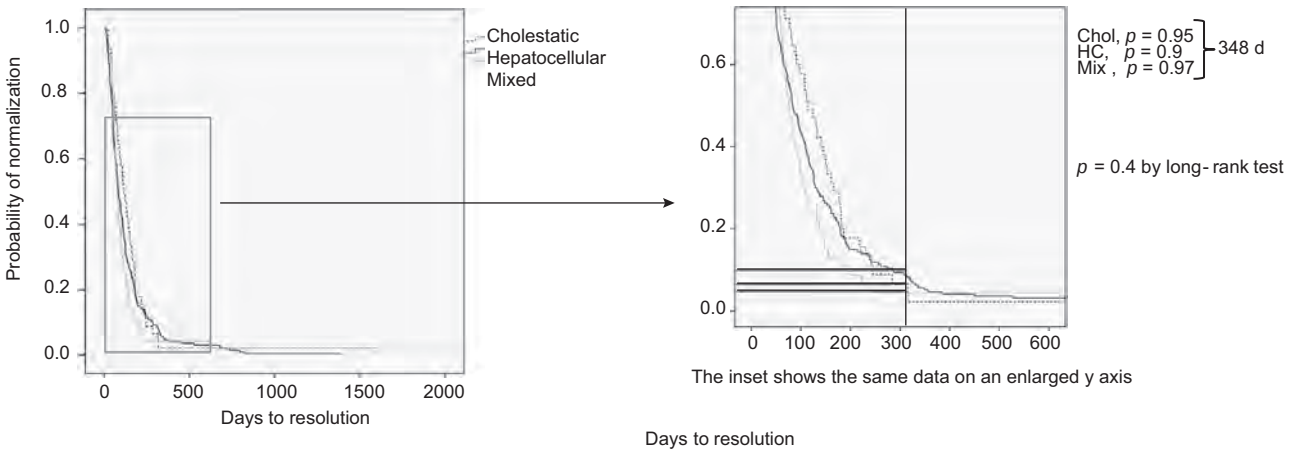
Introduction

Drug-induced liver injury (DILI) is a rare and often unpredictable adverse reaction to many drugs in common use. It represents a leading cause of acute liver failure in Western countries and one of the most common reasons for attrition during drug development and adoption of post-marketing regulatory actions [1].

DILI can present with a wide range of histological findings and phenotypes as a result of the interaction of a drug specific signature with host factors [2,3]. Withdrawal of the offending drug is characteristically followed by resolution of liver damage except for a minor percentage of cases that evolve to fulminant hepatic failure or become chronic.

Analyses of retrospective databases [4] and prospective collaborative networks [5–8] have yielded reliable figures on prognosis of acute DILI and identified risk factors for acute liver failure and liver related-death.

There is a general belief that acute DILI persisting beyond 6 months should be considered chronic, similar to that occurring with viral hepatitis B or C [9]. However, very few studies have addressed the rate of persistence in liver biochemistry alterations after drug discontinuation in patients with acute DILI after longer follow-up. A retrospective evaluation of 33 DILI cases found impaired liver tests or imaging-based evidence of chronic liver disease in 11 of the cases [10]. Furthermore, a retrospective analysis of 685 patients with acute DILI and jaundice found 8 patients who had developed cirrhosis (5 cryptogenic) in a mean follow-up of 10 years [11]. However, the retrospective design of these studies precludes a reliable estimation of the true incidence of chronicity and the resolution time course of biochemical alterations in patients with DILI. Chronic liver injury was initially defined as increases in liver test values >3 months [12]. In a later study, chronicity of cholestatic/mixed type of injury was considered as elevated liver biochemistry values >6 months from DILI onset, assuming that these types of injuries frequently require longer time to resolution [13]. In addition, the United States DILI Network consider chronicity as persistently elevated liver biochemistry on two separate occasions; histological or radiological evidence of persistent liver injury at 6 months or more after DILI



Days to resolution

	0-60	61-90	91-180	181-365	366-730	731-1095	1096-2000	2001-3020
Hepatocellular cases (N = 193)	71	30	57	27	4	3	1	-
Cholestatic cases (N = 46)	9	8	17	10	-	-	2	-
Mixed cases (N = 46)	15	13	12	4	1	-	-	1

Fig. 2. Time to liver injury resolution in 285 patients with acute idiosyncratic drug-induced liver injury who recovered classified by type of damage. An additional 13 patients (not included) had not recovered after 3 years. Chol, cholestatic; HC, hepatocellular; Mix, mixed.

onset [14]. Hence, the best definition of DILI chronicity remains a matter of debate [12–16].

In the present study, we aimed to describe the outcome of prospectively followed patients who survived an acute DILI episode with an emphasis on the time course of the liver biochemical profile in order to determine the best cut-off point to define chronicity, and search for risk factors related to chronicity and clinical consequences of the chronicity.

Patients and methods

Study design

The study population consisted of idiosyncratic drug-induced liver injury cases included in the Spanish DILI registry founded in April 1994. The operational structure of the registry, data recording and case ascertainment has been reported elsewhere [5]. Case report forms contain full information necessary to ascertain causality: (a) compatible temporal relationship between drug intake and appearance of liver disease; (b) serology biochemical, imaging and histological data to exclude alternative liver diseases; and (c) outcome of liver damage. Cases were identified by clinicians from 30 Spanish hospitals.

The criteria for DILI was initially those established by a group of experts (alanine aminotransferase, ALT >2 times the upper limit of normal (xULN), conjugated bilirubin >2 xULN or combined elevations in aspartate aminotransferase (AST), alkaline phosphatase (ALP) and total bilirubin (TB) provided one of them is above 2 xULN) [12] and later restricted to the consensus criteria adopted in 2011 (ALT $\geqslant$5 xULN, ALP $\geqslant$2 xULN or ALT $\geqslant$3 xULN + TB $\geqslant$2 xULN) [15]. Eighty-four percent of the cases fulfilled these later criteria. The pattern of liver injury was classified based on R ratio values, (ALT/ULN)/(ALP/ULN). Cases were considered hepatocellular (HC) when R $\geqslant$5, cholestatic (Chol) when R $\leqslant$2 and mixed (Mix) when 2 <R <5 according to the criteria of the international consensus meeting for DILI) [12]. Severity was classified as mild, moderate, severe or fatal based on the DILI severity index defined in 2011 [15].

We have defined chronicity as persistent ALT, AST, TB or ALP elevations >1 xULN or imaging or histology data compatible with chronicity (irrespective of laboratory data) after one year from DILI recognition. Patients whose liver enzyme values returned to within laboratory references ranges in less than one year, regardless the type of damage, without chronicity signs previously described were defined as acute. Acute DILI patients were followed at least up to resolution. Chronic DILI patients were followed more than one year.

The definition of dyslipidemia was based on the criteria of the national cholesterol education program's adult treatment panel III (ATPIII): total cholesterol >240 mg/dl, HDL cholesterol <40 mg/dl, LDL cholesterol $\geqslant$160 mg/dl or triglycerides $\geqslant$200 mg/dl [17].

Drugs considered to be implicated in the liver damage were classified according to the anatomical therapeutic classification of the World Health Organization [18]. Only patients with a causality probability score of possible or higher using the Council for International Organizations of Medical Science (CIOMS) scale were included [19].

Study patients

Since 1994 to September 2012, 850 patients with idiosyncratic DILI were considered for potential inclusion in the natural history study, and 351 patients fulfilled all the inclusion criteria (Fig. 1).

Inclusion criteria were:

- Survival of the index episode without a liver transplantation
- DILI cases that reached resolution or DILI cases that did not resolve but had follow-up $\geqslant$1 year after DILI recognition
- During follow-up cases had appointments with biochemical analysis scheduled, at least, every 6 months in the first year and annually in the consecutive years.

In patients with more than one DILI episode, only the last episode has been included in the analysis to avoid that liver profile alterations corresponding to the second episode were confounded with chronicity.

Out of these 351 patients, 53 were further excluded due to:

- Underlying chronic liver disease (viral, alcoholic, metabolic or autoimmune hepatitis or altered basal liver profile of unknown aetiology) and Gilbert syndrome (22 cases),
- Systemic diseases affecting the liver (thyroid, heart disease, HIV infection) (17 cases),
- Miscellaneous causes such as paracetamol overdose and patients with alcohol intake over 40 g/day (14 cases).

The study protocol was approved by the local ethics committee of the coordinating center at the "Virgen de la Victoria" University Hospital in Málaga, Spain, and all the subjects who took part in the study gave informed consent.

Statistical analyses

Variables were examined using descriptive statistics. Bivariate associations were measured using Student *t* test for continuous variables and chi-square test for categorical items. Analysis of variance was used for comparisons of groups.

Where variables did not follow a normal distribution, nonparametric analyses (Kruskal-Wallis test) were performed. A receiver operating characteristic (ROC) curve to test ALP and TB in chronicity prediction was performed. Differences were reported as statistically significant if the p value was less than 0.05. Times to event data are represented as Kaplan-Meier estimates. Actuarial probabilities were calculated using the Kaplan-Meier method and were compared with the use of the log-rank test. Variables that were associated with chronicity in univariate analyses were included as potential covariates in a multiple logistic regression model. All statistical analyses were performed using the SPSS software version 19.0.

Results

Two hundred and ninety-eight DILI patients fulfilled all inclusion and none of exclusion criteria and were included in the study. The overall mean age was 53 years (14–88, years), 167 (56%) were female, and hepatocellular damage predominated (203, 68%). The main causative pharmacological drug group was anti-infectious (40%), followed by musculo-skeletal system (13%), central nervous system (12%), and cardiovascular drugs (11%). The cases were assessed as highly probable (43%), probable (50%) and possible (7%) according to the CIOMS/RUCAM scale.

Establishing the best cut-off point to define chronicity

To determine the best cut-off point for chronicity a Kaplan-Meier estimate of liver injury resolution was performed with the 285 cases that normalized liver tests over time out of the 298 patients included in the study (Fig. 2). According to the type of liver damage, 193 cases (68%) were hepatocellular. Out of these, 101 cases (52%) resolved in the first 3 months, with an additional 57 cases resolving before 6 months and 27 more cases before the first year.

Forty-six cases were cholestatic (16%), out of these 17 resolved in the first 3 months (38%), 17 more cases (38%) resolved between month 3 and 6, and 10 more cases resolved before the first year.

In the remaining 46 mixed cases (16%), 28 (60%) resolved in the first 3 months, 12 between 3 and 6 months and 4 more cases resolved before the first year (Fig. 2). The mean time of resolution for the 285 patients was 142 days [95% CI = 115–170 days]. The median was 86 days (95% CI = 75–97). With respect to time to resolution according to type of liver damage it is important to note that in hepatocellular damage, the median resolution time was 83 days (95% CI = 69–97). Cholestatic patients required longer time to resolution, 115 days (95% CI = 83–147) and in patients with mixed liver damage the median resolution time was 76 days (95% CI = 58–94).

We did not observe any statistically significant differences in the probability of resolution at one year between the different types of liver damage ($p = 0.44$). Within 348 days from DILI recognition 95% of the patients who reached resolution (92% of all study patients) had resolved independent of the type of injury. Hence, in the following analyses patients resolving in $\leqslant$1 year (n = 273) are referred to as acute DILI and those requiring >1 year and also those who do not resolve during the follow-up as chronic (n = 25, 8%). Thus "chronic" is meant to be inclusive of prolonged recovery to normalization and unresolved cases. Unresolved includes patients who developed cirrhosis in the first year which became quiescent.

A flow chart of the study population is shown in Fig. 1. In the acute group 174 patients (64%) had normalized liver tests in their respective defined time frames based on the type of liver injury ($\leqslant$3 months hepatocellular and $\leqslant$6 months cholestatic/mixed) and 99 patients (36%) resolved after this time but before one year. In the chronic group 10 patients had cholestatic/mixed type of damage and 15 patients were hepatocellular. In this group, 8

Table 1. Comparison of demographics, clinical, and laboratory parameters in 298 DILI cases according to the time of resolution.

	Acute, ≤1 year (N = 273)	Chronic, >1 year (N = 25)	p value
Female, n (%)	151 (55)	16 (64)	0.4
Age, mean years (range)	52 (14-88)	63 (30-83)	0.002
Gender-specific age, mean (range)			
Men	54 (17-87)	58 (30-70)	0.5
Women	51 (14-88)	66 (43-83)	<0.001
BMI (kg/m^2), mean (range)	26 (17-36)	26 (19-36)	0.6
Clinical presentation, n (%)			
Jaundice	156 (58)	20 (80)	0.032
Hospital admission	110 (45)	17 (77)	0.004
Hypersensitivity features	78 (29)	9 (36)	0.2
Eosinophilia	53 (20)	8 (32)	0.2
Lymphopenia	22 (14)	5 (21)	0.4
Positive autoantibody titres	51 (23)	4 (16)	0.4
Duration of treatment, mean/median days (range)	79/21 (1-1827)	191/49 (4-1826)	0.2
Time to onset, mean/median days (range)	72/21 (0-1826)	152/30 (0-1828)	0.3
Days of continued exposure to drug after onset of symptoms, mean (range)	21 (1-308)	50 (1-514)	0.3
patients, n (%)	147 (54)	18 (72)	
Type of liver injury, n (%)			0.6
Hepatocellular	185 (68)	15 (60)	
Mixed	44 (16)	4 (16)	
Cholestatic	44 (16)	6 (24)	
Laboratory parameters at onset, mean (range)			
TB (mg/dl)	5 (0.13-33)	7 (0.4-28)	0.1
AST xULN (range)	15 (0.6-197)	13 (1-55)	0.7
ALT xULN (range)	19 (0.6-134)	20 (2.5-71)	0.9
GGT xULN (range)	7 (0.2-49)	14 (0.3-79)	0.08
ALP xULN (range)	1.8 (0.2-16)	3 (0.4-11)	0.05
Outcome, n (%)			
Positive rechallenge, n (%)	12 (4)	2 (8)	0.4
Mean follow-up, months (range)	16 (0.2-166)	54 (16-112)	<0.001
Recovery, mean days (range)	106 (7-357)	935 (385-3020)	<0.001
Severity, n (%)			0.003
Mild + moderate	261 (97)	21 (84)	
Severe	9 (3)	4 (16)	
Associated diseases, n (%)			
Diabetes	27 (10)	7 (28)	0.006
Hypertension	31 (25)	10 (50)	0.019
Dyslipidemia	36 (13)	11 (44)	<0.001

The percentages shown were calculated based on the total number of episodes with available information. Severity index, Mild: elevated ALT/ALP meeting DILI criteria with total bilirubin <2 mg/dl; Moderate: elevated ALT/ALP with total bilirubin $\geqslant$2 g/dl; Severe: elevated ALT/ALP and one of the following: ascites, encephalopathy, international normalization ratio >1,5 and/or other organ failure considered to be due to DILI; Fatal: death or transplantation due to DILI. Hypersensitivity features: presence of one or more positive features such as fever, rash, arthralgia, peripheral eosinophilia or lymphopenia; TB, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transpeptidase; ALP, alkaline phosphatase.

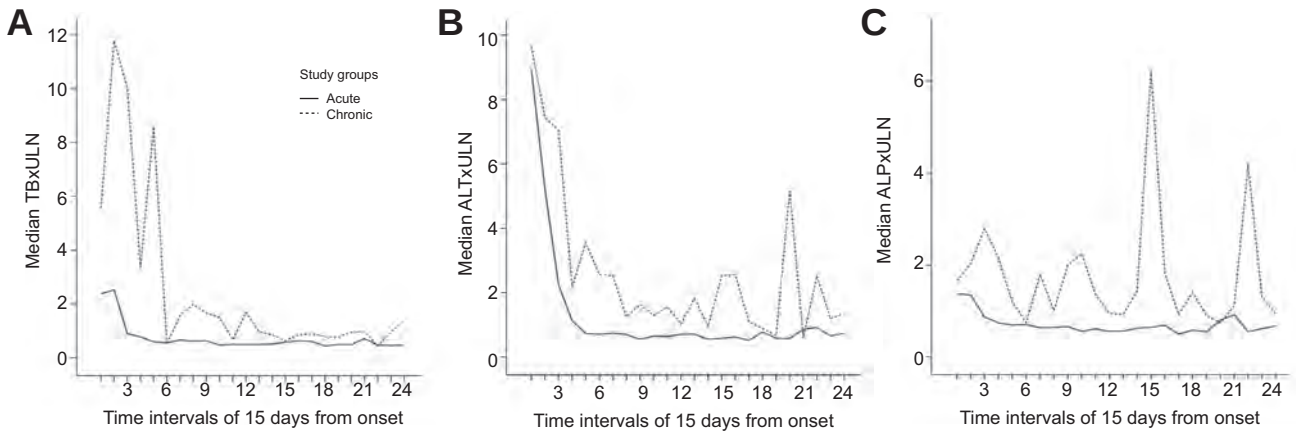


Fig. 3. Median of ALP, ALT and TB values during the first year from DILI onset in acute and chronic groups. Each time interval includes 15 days.

patients (32%) resolved within 3 years from DILI recognition and 16 (64%) did not resolve during the first 3 years of follow-up. After one year from DILI onset one mixed case was lost during follow-up without reaching resolution.

Comparison of demographics, clinical and laboratory parameters between acute and chronic DILI cases

A comparison of demographics, clinical and laboratory parameters between the acute and chronic group is outlined in Table 1.

Mean time of follow-up was 16 months (range: 0.2–166 months) in the acute group and 54 months (range: 16–112 months) in the chronic group. The patients in the chronic group were significantly older as compared to those in the acute group, 63 *vs.* 52 years ($p = 0.002$), with female predominance (64%, $p < 0.001$). Patients who progressed to chronic DILI had a longer duration of treatment (median 49 days compared to 21 days in the acute group), although this difference did not reach statistical significance. The chronic cases presented more frequently with jaundice at onset (80% *vs.* 58%, $p = 0.03$) and more often required hospitalization (77% *vs.* 45%, $p = 0.004$). In addition, the percentage of severe cases was higher in the chronic group compared to patients in the acute group (16% *vs.* 3%, $p = 0.003$). The prevalence of diabetes mellitus, dyslipidemia and hypertension was greater in the chronic group, 28% *vs.* 10% ($p = 0.006$), 44% *vs.* 13% ($p < 0.001$) and 50% *vs.* 25% ($p = 0.019$), respectively. However, body mass index did not differ between the two groups. Furthermore, we analyzed lipid profiles (LDL, HDL, total cholesterol and triglycerides) during follow-ups in 11 chronic (8 on statin and 3 on fibrate treatments) and 36 acute (22 statin and 3 fibrate treatments) dyslipidemic patients, but no differences were found between the groups.

Hepatocellular damage predominated in both the chronic and acute groups (60% *vs.* 68%, respectively, $p = 0.6$). Despite the fact that type of liver injury did not appear as a risk factor for chronicity, the chronic group presented significantly higher mean values of serum ALP (3 xULN *vs.* 1.8 xULN, $p = 0.05$) at DILI onset. Time course of liver biochemistry values revealed that median values of ALP, ALT and TB were higher in the chronic group during the first year. All available laboratory analyses during follow-ups in both the chronic and acute groups are represented in Fig. 3. Table 2 shows demographic, major clinical and serial biochemical parameters of 16 chronic DILI patients who did not resolve in the first 3 years. Additional information about liver profile in the 25 chronic DILI patients is shown in Supplementary Tables 1 and 2. Various time frames were analyzed to explore potential differences in liver tests between the chronic and acute group. In the period 30 to 60 days from DILI onset (second month) significant differences in ALP and TB were found with higher values in the chronic group. We then performed a ROC curve analysis and found that a cut-off point of 1.1 xULN for ALP and 2.8 xULN for TB gave the highest area under the curve (AUC) values to predict chronicity, including slow resolution beyond one year, with a sensitivity of 83% and 75% and a specificity of 87% and 93%, respectively, ($p < 0.001$) (Supplementary Fig. 1).

In the logistic regression analysis, older age [Odds ratio (OR): 1.06, 95% CI: 1.01–1.12; $p = 0.011$], dyslipidemia [OR: 4.26, 95% CI: 1.02–17.74, $p = 0.04$] and severe DILI [OR: 14.22, 95% CI: 2.23–90.9, $p = 0.005$] were found to be independent risk factors for chronic DILI development.

Comparison of demographics and clinical characteristics of the 25 chronic patients according to type of liver damage are presented in Table 3. Liver biopsy was available for 16 patients (64%) in the chronic group, showing two cases with ductal lesion, one with low grade fibrosis and seven with cirrhosis. Drugs related to liver cirrhosis were atorvastatin, bentazepam, ebrotidine, clopidogrel/atorvastatin, amoxicillin-clavulanate/ibuprofen and ranitidine. Out of the seven biopsies of DILI cases that evolved to cirrhosis, only one showed steatosis, but not steatohepatitis, in a biopsy performed one year after the onset of the DILI episode. There were three more cases with steatosis demonstrated in the liver biopsies in the chronic group during the follow-up (performed from month 8 to 60 after DILI onset), two of these had previous biopsies without this finding (Supplementary Tables 1 and 2 show details for individual patients).

Therapeutics Groups involved in chronic DILI

Among the culprit therapeutic drug classes involved in chronic DILI episodes, the more frequent were statins (24%), anti-infectives (24%, including 16% amoxicillin-clavulanate cases and 8% sulfamethoxazole and trimethoprim) and H_2-receptor antagonists (12%), mainly due to ebrotidine, a drug marketed in Spain in 1997 and withdrawn in 1998 (Table 4). Interestingly, the angiotensin converting enzyme inhibitors and angiotensin II antagonists group was only represented in the chronic group.

Table 2. Demographic, major clinical and serial biochemical parameters of 16 DILI patients who required more than three years to resolve or did not resolve.

Case	Age/sex	Comorbidities	Type of liver injury	Liver profile	3-6 months (xULN)	0.5-1 year (xULN)	1-2 years (xULN)	2-3 years (xULN)	>3 years (xULN)
1** Atorvastatin	67/F	Diabetes Arterial hypertension Ischemic cardiopathy Dyslipidemia	HC	TB AST ALT GGT ALP	5.1 8 11 16 1.2	1 2.5 3.1 2.9 1.1	0.7 0.5 1 3 0.9		
7 Amoxicillin-clavulanate	83/F	Arterial hypertension Dyslipidemia	HC	TB AST ALT GGT ALP	1.4 0.7 0.5 0.7 0.9	0.8 1.2 0.5 0.7 2.2	0.8 1.2 0.8 0.2 0.7	0.7 1.8 1.5 0.4 0.7	
9 Flutamide	65/M	Prostate cancer Tuberculosis	HC	TB AST ALT GGT ALP	- 0.7 1.2 1.3 -		1.3 0.7 0.7 1.2 0.5	1.4 0.7 0.8 0.5 0.4	0.8 0.7 0.9 0.5 0.4
10 Levonorgestrel and estrogen	43/F	Cholestasis of pregnancy	HC	TB AST ALT GGT ALP	0.5 0.6 1.3 0.3 0.4	*	*	0.5 0.7 1.3 0.4 -	0.8 0.8 1.1 0.1 0.2
11** Bentazepam	60/F	Uterine myoma Cardiopathy Depression Arterial hypertension	HC	TB AST ALT GGT ALP	3.3 1.5 1.2 3.6 0.8	1.1 1.05 0.7 2 0.4			
13** Ebrotidine	55/F	Diabetes Arterial hypertension Arthrosis	HC	TB AST ALT GGT ALP	0.9 0.8 1.2 1.5 1.3	0.6 0.5 0.6 0.6 1.05	0.8 0.6 0.4 0.5 1.07	*	0.3 0.4 0.4 0.8 1.3
14** Ebrotidine	69/F	None	HC	TB AST ALT GGT ALP	1.1 0.5 0.3 0.2 0.4	1.3 0.9 0.8 0.7 0.7	1.7 0.6 0.5 0.3 0.5	1.5 0.8 0.5 0.3 0.5	1.1 0.5 0.3 0.2 0.4
15** Clopidogrel/ atorvastatin	60/M	Diabetes Arterial hypertension Cardiopathy Dyslipidemia	HC	TB AST ALT GGT ALP	2.4 1.3 2.1 38 2.7	0.9 1.5 2 20 1.8	0.9 1.5 2 20 1.7		
18 Amoxicillin-clavulanate/ carbamazepine	65/M	Brucellosis Trigeminal neuralgia	Chol	TB AST ALT GGT ALP	1.8 2 2.7 10 2.5	1.2 0.9 1.3 7.6 1.2	1.6 0.9 1 3.9 1.2	1.2 0.6 0.7 1.2 0.5	0.8 0.6 0.5 0.6 0.7
19 Fenofibrate/ raloxifene	60/F	Colorectal cancer Dyslipidemia Osteoporosis	Mix	TB AST ALT GGT ALP	0.4 2.8 2.5 40 11.5	0.4 1.5 1.3 23.5 4.3	0.4 1.3 1.1 9.3 3	- 1.1 0.9 4.6 1	0.3 3.0 1.6 24 5.0
20 Thiamazole	78/F	Hyperthyroidism Goiter	Chol	TB AST ALT GGT ALP	1.1 0.6 0.6 2.4 1.6	*	*	*	1.0 0.7 0.4 0.5 1.0

Discussion

Up to now there are scarce and heterogeneous data reported on the long-term outcome of patients who survived an acute DILI episode, reflecting differences in the methodological approaches and the broad definitions of chronic DILI used in previous studies as outlined in Table 5.

We here present a large prospective cohort of patients with DILI caused by a variety of agents with the longest follow-up reported in an attempt to better characterize chronic outcome

Table 2 (*Continued*)

Case	Age/sex	Comorbidities	Type of liver injury	Liver profile	3-6 months (xULN)	0.5-1 year (xULN)	1-2 years (xULN)	2-3 years (xULN)	>3 years (xULN)
21 Gemfibrozil/ lovastatin	63/F	Dyslipidemia Diabetes Osteoarthrosis	Chol	TB AST ALT GGT ALP		0.4 1.2 1.4 24 2.3	0.4 0.8 0.8 22 2.1	- 0.3 0.8 19 2.4	0.3 0.7 0.5 9.0 1.9
22** Amoxicillin-clavulanate/ ibuprofen	70/M	Arterial hypertension	Chol	TB AST ALT GGT ALP	1.7 3 2.4 16 4.1	1.3 1.7 1.7 7 2.2	1.4 1.6 1.3 5.5 2.3	0.8 1.4 1.2 1 1.3	1.8 1.0 0.7 0.9 1.0
23 Ibuprofen	40/M	None	Chol	TB AST ALT GGT ALP	0.6 1.3 4.3 15 6.2	- 1 1.5 8.6 0.9	- 3.1 - 7.6 0.8	- 1.2 1.5 4.2 -	0.8 1.0 1.2 4.0 0.7
24** Ranitidine	54/F	Diabetes Arterial hypertension Dyslipidemia	Chol	TB AST ALT GGT ALP	0.4 1.8 2.5 53 4.2		- 1.8 1.6 - 2.6	0.9 2.8 4.7 61 3.7	0.4 1.8 1.3 21 4.0
25 Atorvastatin	75/F	Dyslipidemia Venous insufficiency	Mix	TB AST ALT GGT ALP	1.9 3 3.1 15 5.8	0.2 1.5 1.1 4.4 1.5	0.5 1.1 1.08 1.9 1.4	0.3 1.4 1.03 2.8 1.4	0.3 0.7 0.5 1.3 0.7

TB, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transpeptidase; ALP, alkaline phosphatase; ULN, upper limit of normal; Chol, cholestatic damage; HC, hepatocellular damage; Mix, mixed damage.
*Altered liver profile reported in clinical history (laboratory data are not available).
**The patient developed cirrhosis.

Table 3. Comparison of demographics and clinical characteristics of the 25 chronic patients according to the type of liver damage.

	Hepatocellular N = 15	Cholestatic/mixed N = 10
Age years, mean (range)	62 (30-83)	64 (40-78)
Female, n (%)	9 (60)	7 (70)
Jaundice, n (%)	13 (87)	7 (70)
Hypersensitivity features, n (%)	3 (20)	6 (60)
Liver biopsy*, n (%)	10 (67)	6 (60)
Fibrosis, n (%)	1 (7)	0
Cirrhosis, n (%)	5 (33)	2 (20)
Ductal lesion, n (%)	0	2 (20)
Steatosis, n (%)	2 (13)	2 (20)
Biochemical normalization ≤3 years, n (%)	7 (47)	1 (10)

Hypersensitivity features: Presence of one or more positive features such as fever, rash, arthralgia, peripheral eosinophilia or lymphopenia. The time of biopsy performances varies from 2 weeks to 60 months after DILI onset.

in DILI. Although our study had strict inclusion and exclusion criteria in order to avoid confounding factors, it indeed reflects a real clinical practice setting.

The first international consensus meeting on DILI recommended that a hepatocellular pattern of liver injury persisting for more than 3 months after onset should be considered as chronic liver injury [12]. This period of resolution nowadays seems inappropriate when analyzing the outcome of large cohorts of DILI patients, which have shown that many subjects with hepatocellular damage have persistent elevations in liver enzymes at this time point. The drug induced liver injury network (DILIN) group has used in their analysis the standard period of six months to establish chronicity [7,8]. In a consensus of experts in 2011 [15] continued liver damage was classified as persistent DILI when there was evidence of liver injury 3 and 6 months after withdrawal of the culprit drug in hepatocellular and cholestatic type of liver injury, respectively. Chronic DILI was then defined as evidence of continued liver injury beyond 12 months of follow-up after withdrawal of the causative drug. In the present study, encompassing a large and well-phenotyped DILI cohort in which potential confounding alternative causes of persistent damage were thoroughly excluded, shows, via Kaplan-Meier analysis, that 95% of the DILI patients who finally recovered had resolved the injury at 348 days regardless the type of damage. Therefore, we do not consider it necessary to further classify the acute group into persistent and chronic as done by Aithal *et al.* [15]. Hence, we consider one year as the best cut-off point to discriminate acute DILI patients from those with very prolonged resolving damage or true chronic DILI.

It is a general belief [13,20] that cholestatic and mixed damage require longer time to normalize. Our data challenge this view as the median days to resolution were 83, 115 and 76 days for hepatocellular, cholestatic and mixed cases, respectively, with no statistically significant differences among the groups ($p = 0.4$). Hence, our findings indicate that it is not necessary to consider different times of resolution based on the type of liver injury in the definition of chronicity.

Table 4. Comparison of drug classes implicated in DILI cases between acute (resolution ⩽1 year) and chronic (persistent >1 year) patients.

	Acute, ≤1 year (N = 273)	Chronic, >1 year (N = 25)	*p* value
Drug classes, n (%)			
H2-receptor antagonists*	6 (2)	3 (12)	0.03
Antithrombotic agents	3 (1.1)	1 (4)	0.8
ACE inhibitors + angiotensin II antagonists	0	2 (8)	0.0007
Statins	18 (6)	6 (24)	0.002
Fibrates	3 (1.1)	2 (8)	0.07
Female sex hormones	7 (3)	2 (8)	0.36
Antithyroid preparations	3 (1.1)	1 (4)	0.8
Anti-infectives			
Penicillins-cephalosporins (excluding AC)	6 (2)	0	0.9
Amoxicillin-clavulanic acid (AC)	68 (25)	4 (16)	0.4
Sulfamethoxazole and trimethoprim	2 (0.7)	2 (8)	0.03
Fluoroquinolones	11 (4)	0	0.6
Macrolides	8 (3)	0	0.8
Antineoplastic agents	5 (1.8)	1 (4)	0.9
Antiandrogens	4 (1.5)	1 (4)	0.9
Immunosuppressants	5 (1.8)	0	0.9
Non-steroidal antiinflammatory drugs (NSAIDs)	41 (15)	2 (8)	0.5
Tetrabamate* *	4 (1.5)	1 (4)	0.9
Antiepileptics	6 (2)	2 (8)	0.3
Herbal products	12 (4)	0	0.6

*Mainly due to Ebrotidine a drug withdrawn from the Spanish market in 1998.
**Tetrabamate contains the combination of two carbamates (febarbamate and difebarbamate) and phenobarbital. It was withdrawn from the Spanish market in 2002.
ACE inhibitors, angiotensin-converting enzyme inhibitors; NSAIDs, non-steroidal antiinflammatory drugs.

The prevalence of chronic DILI beyond one year follow-up in this study was 8%. It is lower than the prevalence previously reported by Aithal *et al.* in 1999 (33%) [10], and the DILIN group (13.9%-18.9%) [7,8,16]. These differences can be explained by the diverse definitions of chronicity used (6 months *vs.* 1 year) and less restrictive study inclusion criteria (Table 5). Furthermore, our study was not designed to search for prevalence of chronic DILI as the strict exclusion criteria (mainly loss of follow-up in the first year before complete resolution) do not allow us to know the true prevalence in the whole cohort of DILI patients included in the registry. In addition, in our study we paid attention to potential confounding factors, excluding not only patients with pre-existing chronic liver disease but also patients with systemic or any other diseases affecting the liver. However, as all chronic DILI cases do not have the same clinical impact, we could classify them into three broad categories: early cirrhosis that becomes quiescent, slow resolvers who do not progress to cirrhosis and cases with persistent activity (including borderline liver laboratory parameters) that may need monitoring but are not major clinical problems. Considering these distinctions and our data, one could question if chronic DILI with active liver injury is a true phenomenon *vs.* simply reflecting very slow course to complete recovery. The few cases beyond three years' follow-up with low grade liver test abnormalities cannot be distinguished from background incidence of these changes in the general population.

Various risk factors have been associated with chronic DILI. In the present study, mean age was significantly higher in the chronic group, especially in women, showing that older DILI women have a higher tendency towards chronicity. It could be speculated that aging results in declining of autophagy and progressive loss of cellular repair and regeneration capacity. Autophagy is being recognized as a critical function in the clearance of protein adducts, removal of damaged organelles and modulation of immune tolerance [21]. Furthermore, female gender has been demonstrated to be more susceptible towards acute liver failure [6,22], showing that perhaps women have greater difficulty in repairing liver damage. In previous studies (Table 5), female gender also predominated in chronic DILI populations [8,10,13,16,20]. However, our chronic patients were older than previously reported [16].

The presence of metabolic risk factors such as diabetes, dyslipidaemia and hypertension, were found to be more frequent in the chronic group. In this setting, it is difficult to distinguish between persistent liver damage due to chronic DILI and underlying non-alcoholic fatty liver disease. Previous studies have also found diabetes to be more frequent in chronic DILI patients [8,16]. Our findings are consistent with the fact that older age is a risk factor for chronicity and in the elderly metabolic risk factors are more prevalent. Ultimately, diabetes, dyslipidemia and hypertension along with the age in an elderly subject could compromise the repair of the liver damage favoring a chronic outcome. Interestingly, dyslipidemia was found to be protective from fulminant outcome in a previous study, and we speculate that this effect could be indirectly related to the use of statins [6]. Statins were the most frequent drug group found in the chronic cases compared to acute cases in the present analysis. However, it is possible that this result is a reflection of the underlying dyslipidemia. The precise mechanism of statin-induced chronic DILI is unknown but could involve an immune self-perpetuating response as these drugs have been increasingly associated with drug-induced autoimmune hepatitis [23].

Patients with more severe acute DILI episodes, presenting with jaundice and requiring hospitalization, also had an increased risk of chronicity, suggesting that the time to resolution is longer when the damage is more severe. Liver function alterations can take longer time to resolve than just mild transaminase elevations. Hospitalization has been previously observed as risk factor for chronic DILI [8].

Another interesting finding was significantly increased ALP values at DILI onset which is coincidental with the study by Fontana *et al.* [16]. ALP elevations are generally associated with cholestatic damage. However, although cholestatic and mixed damage were more frequent in chronic DILI patients than in acute DILI patients, there were no significant differences among the types of liver injury. Furthermore, cholestatic damage has been demonstrated to be associated with older age [2]. During follow-up median values of ALP as well as TB were higher in the chronic group. In addition, in the second month from DILI onset, ALP >1.1 xULN and TB >2.8 xULN values were the best cut-off points to predict chronicity in DILI (Supplementary Fig. 1). This finding could have a prognostic value in clinical practice. The reason for selecting the second month from DILI onset was that this time frame had a higher number of available laboratory test than the later ones, and this time frame demonstrated higher differences in the studied parameters between the groups. Hence, we consider the second month to be an appropriate period for a prognostic evaluation in clinical practice.

Table 5. Studies addressing the long-term outcome of idiosyncratic drug-induced liver injury.

Study (DILI criteria)	Chronicity criteria	Follow-up	Proportion chronicity	Mean age, yr/female %	Culprit drugs	Reference
Retrospective database/histology study (ALT>2 xULN, CB>2 xULN or combined elevations in AST, ALP and TB provided one of them is above 2 xULN)	Biochemical, radiological or histological evidence of liver injury >12 months	Median 5 years	11/33* (33%)	49/59%	Antibiotics NSAIDs Psycholeptics	Aithal *et al.*, Gut 1999 [10]
Prospective registry study (ALT>2 xULN, CB>2 xULN or combined elevations in AST, ALP and TB provided one of them is above 2 xULN)	Persistent biochemical abnormality of HC>3 months after drug withdrawal or >6 months after chol/mix damage	Mean 20 months	28/493 (5.7%)	55/64%	Cardiovascular drugs (captopril, atorvastatin) and CNS drugs (bentazepam)	Andrade *et al.*, Hepatology 2006 [13]
Retrospective database study (ALT>2 xULN, CB>2 xULN or combined elevations in AST, ALP and TB provided one of them is above 2 xULN, excluding ALF)	Persistent abnormality at follow-up at least 3 months after stopping drug treatment for HC and at least 6 months for chol/mix	Median 48 months	3/50 (6%)	49/67%	Antibiotics (nitrofurantoin, flucoxacillin, clindamycin)	Björnsson *et al.*, AP&T 2007 [21]
Prospective registry study (ALT>5 x ULN, ALP>2 xULN, INR>1.5 or TB>2.5 mg/dl with ALT, AST or ALP>1 xULN)	Persistent liver-related laboratory, radiologic, or histologic abnormalities at 6 months after DILI recognition	>6 months	41/300 (13.6%)	n.a.	n.a.	Chalasani *et al.*, Gastroenterology 2008 [7]
Retrospective database study (ALT>2 xULN, CB>2 xULN or combined elevations in AST, ALP and TB provided one of them is above 2 xULN)	Morbidity/mortality after DILI hospitalization	Mean 11 years	23/685 (3.4%)**	n.a.	n.a.	Björnsson *et al.*, J Hepatol 2009 [11]
Prospective registry study (AST or ALT>5 xULN, ALP>2 xULN, INR>1.5 or TB>2.5 mg/dl)	Persistently elevated AST, ALT, ALP or TB, histological evidence of ongoing liver injury, or radiological evidence of persistent liver injury ≥6 months after DILI onset	Mean 24 months	113/598 (18.9%)	49.7/ 67.3%	Antimicrobial, HDS, cardiovascular drugs, antineoplastic	Fontana *et al.*, Gastroenterology 2014 [8]
Prospective registry study (AST or ALT>5, ALP>2 xULN, INR>1.5 or TB>2.5 mg/dl)	Persisters: ALP >ULN or AST, ALT>1.5 xULN at 12 months after DILI onset	Mean 24 months	74/598 (12%)	52.6/ 69%	Antimicrobial, antineoplastic, cardiovascular, HDS	Fontana *et al.*, Am J Gastroenterol 2015 [16]

*7 patients failed to attend follow-up and 4 died.
**5 patients had liver-related death.
n.a., not available; TB, total bilirubin; CB, conjugated bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; HDS, herbals and dietary supplements; Chol, cholestatic damage; HC, hepatocellular damage; Mix, mixed damage.

In the chronic group seven cases developed cirrhosis. Two hepatocellular cases were related to ebrotidine (a histamine H_2-receptor antagonist), which has been discontinued in Spain since 1998 because of its hepatotoxic potential with cases reported having rapid progression to cirrhosis [24,25]. Other cases were related to bentazepam, atorvastatin and clopidogrel/atorvastatin. Two other patients with cirrhosis were cholestatic cases, one due to amoxicillin-clavulanate/ibuprofen and another induced by ranitidine. Liver cirrhosis due to amoxicillin-clavulanate, bentazepam, and atorvastatin has also been reported previously [13,26,27], while ranitidine has been associated with the development of autoimmune hepatitis [28].

We cannot rule out that some chronic DILI patients who did not resolve during the follow-up period had pre-existing non-alcoholic steatohepatitis (NASH). However, the majority of chronic patients had no signs of steatosis on ultrasound examinations, four patients had normal liver tests at baseline, and 12 out of 16 biopsies did not show any indications of steatosis (see Supplementary Tables 1 and 2). The remaining four biopsies showed steatosis during the evolution of the episode, with normal initial ultrasound or normal basal liver profile. Besides, two of these patients with steatosis in the biopsy had a cholestatic liver damage, not attributable to an underlying NASH. Alternatively, the absence of resolution of the chronic DILI patients could be attributed to the development of NASH, during the follow-up of the DILI episode which could be induced or not by the drug, as this group of chronic patients share risk factors with NASH patients. Currently it is not feasible to differentiate these two situations. Furthermore, the non-inclusion of nearly 500 patients due to loss of follow-up could have introduced selection bias as many of these patients were probably acute cases.

Many of the drugs involved in chronicity in our study have previously been described in the literature with regards to chronicity. Published studies associated with development of chronic liver disease and cirrhosis include: isoniazid [29], nitrofurantoin [30–32], flucloxacillin [33], amiodarone [34], methotrexate [35], chlorpromazine [36], ramipril [37], diclofenac [38], statins [13,39,40] sulphonamides and trimethoprim (TMP/SMZ) [41–43], fenofibrate [44], amoxicillin-clavulanate [43], oral contraceptives [45] and terbinafine [46,47].

Herein we demonstrate that the more reliable cut-off time point for definition of chronic DILI is one year after onset of the acute toxic liver disease. Ninety-two per cent of patients resolved by one year and therefore this cut-off identifies patients who need further follow-up. The main risk factors for chronic DILI are older age, dyslipidaemia, and severity of the acute episode. We conclude that aside from a small number of cases of early onset cirrhosis which becomes quiescent, gradual resolution at 1 or 3+ years or persistence of borderline laboratory abnormalities beyond 3 years is seen in a very small percentage of cases. The persistence of these very mild abnormalities is of uncertain significance but does not appear to be an important clinical problem. Hence, the term "chronic" is somewhat controversial as there are "chronic DILI patients" who eventually resolve the liver damage. However, we have used this term to differentiate it from "acute DILI", as we do not think it is appropriate to use the term "acute damage" when requiring more than one or even more than three years to resolve. Nevertheless, it is prudent to document resolution in follow-up and therefore identification of the risk of slow resolution or persistence determined by early laboratory changes (at two months) is of practical value in flagging cases for closer long-term scrutiny. Our data is the most detailed long-term follow-up of acute DILI and indicates that chronic (active) DILI is extremely rare.

Financial support

The present study has been supported by grants of the Instituto de Salud Carlos III co-founded by Fondo Europeo de Desarrollo Regional – FEDER (contract numbers: PI04/1688, PI12-00620, AC-0073-2013) and by the Agencia Española del Medicamento. CIBERehd is funded by Instituto de Salud Carlos III. The funding sources had no involvement in the study design; in the collection, analysis, and interpretation of data; in the writing of the report or in the decision to submit the manuscript for publication.

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Authors' contributions

Designed the study: IMC, MRD, NK, MIL and RJA. Acquisition of data: MRD, MIL, RJA, IMC, AGJ, MGC, AOA, JSC, IM, BGM, MCF, MRG, JMN, AMB, EM, HH, SB, GS, ER, EGD, AC, EMZ, MJP, JMM, AAP, MHG, MP, MEZ. Analyzed data: IMC, MRD, BGM and AGJ. Wrote the manuscript: IMC, MRD, NK, BGM, CS, MGC, MIL and RJA.

Acknowledgments

The authors are grateful to D. Ramon Hidalgo of the Servicio Central de Informatica de la Universidad de Málaga for his invaluable help in the statistical analyses. We would like to acknowledge the following participating clinical centres on behalf of the Spanish group for the Study of Drug-Induced Liver Disease: Hospital Universitario Virgen de la Victoria, Málaga (coordinating center): RJ Andrade, MI Lucena, C Stephens, M García-Cortés, M Robles-Díaz, I Medina-Cáliz, J Sanabria, B García-Muñoz, R Alcántara, I Moreno, A González-Jimenez, A Papineau, A Ortega-Alonso; Hospital Regional Universitario de Málaga: M Jiménez-Pérez, R González-Grande; Hospital Torrecárdenas, Almería: MC Fernández, G Peláez, M Casado, M González-Sánchez; Hospital Universitario Virgen de Valme, Sevilla: M Romero-Gómez, R Calle-Sanz, R Millan-Domínguez, B Fombuena, R Gallego, L Rojas, A Rojas, J Ampuero, JA del Campo A Gil-Gómez, E Vilar; Hospital de Mendaro, Guipúzcoa: A Castiella, EM Zapata, L Zubiaurre; Hospital Central de Asturias, Oviedo: R Pérez-Álvarez, L Rodrigo-Sáez.

Hospital Costa del Sol, Marbella (Málaga): JM Navarro, IM Mendez-Sánchez, A Chaves; Hospital Sant Pau, Barcelona: G Soriano, C Guarner, EM Román; Hospital Morales Meseguer, Murcia: H Hallal, E García-Oltra, JC Titos-Arcos, A Pérez-Martínez, C Sánchez-Cobarro, JM Egea-Caparrós; Hospital de Donosti, San Sebastián: J Arenas, MI Gómez-Osua, A Gómez-García, FJ Esandi; Hospital de Basurto, Bilbao: S Blanco, P Martínez-Odriozola; Hospital Alto Deba Mondragón, Guipúzcoa: P Otazua; Hospital Universitario San Cecilio, Granada: J Salmerón, A Gila; Hospital Clínico Valladolid: JM González, S Lorenzo; Hospital La Fe, Valencia: M Prieto, I Conde-Amiel, M Garcia-Eliz, M Berenguer; Hospital de Sagunto, Valencia: J Primo, JR Molés, A Garayoa; Hospital de Laredo, Cantabria: M Carrascosa; Hospital 12 de Octubre, Madrid: E Gómez- Domínguez; Hospital Germans Trias i Pujol, Badalona, Barcelona: E Montané, AL Arellano, M Farré, AM Barriocanal, Y Sanz; Hospital Clínic, Barcelona: M Bruguera, P Gines, S Lens, JC García; Hospital Universitario de Canarias, La Laguna, Tenerife: A Aldea-Perona, M Hernández-Guerra, M Moreno-San Fiel, C Boada-Fernández del Campo; Hospital Infanta Elena, Valdemoro, Madrid: M Tejedor; Hospital de Alcorcón, Alcorcón, Madrid: C Fernández, M Fernández-Gil; Hospital Reina Sofía, Córdoba: JL Montero, M de la Mata; Hospital Miguel Servet, Zaragoza: J Fuentes-Olmo, EM Fernández-Bonilla; Complejo Hospitalario Universitario de Albacete, Albacete: JM Moreno, P Martínez-Rodenas, M Garrido; Hospital Xeral Calde, Lugo: S Ávila; Hospital Virgen de las Nieves, Granada: F Nogueras; Hospital Puerta de Hierro, Madrid: J de la Revilla, M Trapero, M Gómez; Hospital Quirón de Marbella, Málaga: VM Aguilar, M De Sola; Hospital Puerta del Mar, Cádiz: P Rendón; Hospital Parc Taulí de Sabadell, Barcelona: M Vergara, J Sánchez Delgado; Hospital Arnau de Villanova, Valencia: O González-López; Hospital Carlos III, Madrid: J García-Samaniego, A Madejón; Hospital de Galdakao: JL Cabriada; Hospital Marqués de Valdecilla, Santander: J Crespo.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jhep.2016.05.003.

References

[1] Kaplowitz N. Idiosyncratic drug hepatotoxicity. Nat Rev Drug Discov 2005;4:489–499.
[2] Lucena MI, Andrade RJ, Kaplowitz N, García-Cortes M, Fernández MC, Romero-Gomez M, et al. Phenotypic characterization of idiosyncratic drug-induced liver injury: the influence of age and sex. Hepatology 2009;49:2001–2009.

[3] Kleiner DE, Chalasani NP, Lee WM, Fontana RJ, Bonkovsky HL, Watkins PB, et al. Hepatic histological findings in suspected drug-induced liver injury: systematic evaluation and clinical associations. Hepatology 2014;59:661–670.

[4] Björnsson E, Olsson R. Outcome and prognostic markers in severe drug-induced liver disease. Hepatology 2005;42:481–489.

[5] Andrade RJ, Lucena MI, Fernández MC, Pelaez G, Pachkoria K, García-Ruiz E, et al. Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish registry over a 10-year period. Gastroenterology 2005;129:512–521.

[6] Robles-Diaz M, Lucena MI, Kaplowitz N, Stephens C, Medina-Cáliz I, González-Jimenez A, et al. Use of Hy's law and a new composite algorithm to predict acute liver failure in patients with drug-induced liver injury. Gastroenterology 2014;147:109–118.

[7] Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, et al. Causes, clinical features and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterology 2008;135:1924–1934.

[8] Fontana RJ, Hayashi PH, Gu J, Reddy KR, Barnhart H, Watkins PB, et al. Idiosyncratic drug-induced liver injury is associated with substantial morbidity and mortality within 6 months from onset. Gastroenterology 2014;147:96–108.

[9] Seeff LB. Drug-induced chronic liver disease, with emphasis on chronic active hepatitis. Semin Liver Dis 1981;1:104–115.

[10] Aithal PG, Day CP. The natural history of histologically proved drug induced liver disease. Gut 1999;44:731–735.

[11] Björnsson E, Davidsdottir L. The long-term follow-up after idiosyncratic drug-induced liver injury with jaundice. J Hepatol 2009;50:511–517.

[12] Benichou C. Criteria of drug-induced liver disorders. Report of an International Consensus Meeting. J Hepatol 1990;11:272–276.

[13] Andrade RJ, Lucena MI, Kaplowitz N, García-Muṇoz B, Borraz Y, Pachkoria K, et al. Outcome of acute idiosyncratic drug-induced liver injury: long-term follow-up in a hepatotoxicity registry. Hepatology 2006;44:1581–1588.

[14] Fontana RJ, Watkins PB, Bonkovsky HL, Chalasani N, Davern T, Serrano J, et al. Drug-Induced Liver Injury Network (DILIN) prospective study: rationale, design and conduct. Drug Saf 2009;32:55–68.

[15] Aithal GP, Watkins PB, Andrade RJ, Larrey D, Molokhia M, Takikawa H, et al. Case definition and phenotype standardization in drug-induced liver injury. Clin Pharmacol Ther 2011;89:806–815.

[16] Fontana RJ, Hayashi PH, Barnhart H, Kleiner DE, Reddy KR, Chalasani N, et al. Persistent liver biochemistry abnormalities are more common in older patients and those with cholestatic drug induced liver injury. Am J Gastroenterol 2015;110:1450–1459.

[17] Expert panel on detection, evaluation, and treatment of high blood cholesterol in adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). JAMA 2001;285:2486–2497.

[18] Word Health Organization Collaborating Center for drugs statistics methodology. Guidelines for Anatomical Therapeutic Chemical (ATC) classification and defined daily dose (DDD) assignment. Oslo, Norway: World Health Organization Collaborating Center for Drug statistics methodology; 2014.

[19] Danan G, Benichou C. Causality assessment of adverse reactions to drugs I. A novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries. J Clin Epidemiol 1993;46:1323–1330.

[20] Björnsson E, Kalaitzakis E, Av Klinteberg V, Alem N, Olsson R. Long-term follow-up of patients with mild to moderate drug-induced liver injury. Aliment Pharmacol Ther 2007;26:79–85.

[21] Williams CD, Jaeschke H. Role of innate and adaptive immunity during drug-induced liver injury. Toxicol Res 2012;1:161–170.

[22] Reuben A, Koch DG, Lee WM. Drug-induced acute liver failure: results of a U. S. multicenter, prospective study. Hepatology 2010;52:2065–2076.

[23] Lucena MI, Kaplowitz N, Hallal H, Castiella A, García-Bengoechea M, Otazua P, et al. Recurrent drug-induced liver injury (DILI) with different drugs in the Spanish Registry: the dilemma of the relationship to autoimmune hepatitis. J Hepatol 2011;55:820–827.

[24] Andrade RJ, Lucena MI, Martin-Vivaldi R, Fernandez MC, Nogueras F, Pelaez G, et al. Acute liver injury associated with the use of ebrotidine, a new H2-receptor antagonist. J Hepatol 1999;31:641–646.

[25] Pineda JA, Larrauri J, Macías J, Hernández A, Guijarro J, Sayago M, et al. Rapid progression to liver cirrhosis of toxic hepatitis due to ebrotidine. J Hepatol 1999;31:777–778.

[26] Andrade RJ, Lucena MI, Aguilar J, Lazo MD, Camargo R, Moreno P, et al. Chronic liver injury related to use of bentazepam: an unusual instance of benzodiazepine hepatotoxicity. Dig Dis Sci 2000;45:1400–1404.

[27] Perdices EV, Medina-Cáliz I, Hernando S, Ortega A, Martín-Ocaña F, Navarro JM, et al. Hepatotoxicity associated with statin use: analysis of the cases included in the Spanish Hepatotoxicity Registry. Rev Esp Enferm Dig 2014;106:246–254.

[28] Luparini RL, Rotundo A, Mattace R, Marigliano V. Possibly ranitidine-induced autoimmune hepatitis. Ann Ital Med Int 2000;15:214–217.

[29] Black M, Mitchell JR, Zimmerman HJ, Ishak KG, Epler GR. Isoniazid-associated hepatitis in 114 patients. Gastroenterology 1975;69:289–302.

[30] Sharp JR, Ishak KG, Zimmerman HJ. Chronic active hepatitis and severe hepatic necrosis associated with nitrofurantoin. Ann Intern Med 1980;92:14–19.

[31] Amit G, Cohen P, Ackerman Z. Nitrofurantoin-induced chronic active hepatitis. Isr Med Assoc J 2002;4:184–186.

[32] Stricker BH, Blok AP, Claas FH, Van Parys GE, Desmet VJ. Hepatic injury associated with the use of nitrofurans: a clinicopathological study of 52 reported cases. Hepatology 1988;8:599–606.

[33] Olsson R, Wiholm BE, Sand C, Zettergren L, Hultcrantz R, Myrhed M. Liver damage from flucloxacillin, cloxacillin and dicloxacillin. J Hepatol 1992;15:154–161.

[34] Oikawa H, Maesawa C, Sato R, Oikawa K, Yamada H, Oriso S, et al. Liver cirrhosis induced by long-term administration of a daily low dose of amiodarone: a case report. World J Gastroenterol 2005;11:5394–5397.

[35] Whiting-O'Keefe QE, Fye KH, Sack KD. Methotrexate and histologic hepatic abnormalities: a meta-analysis. Am J Med 1991;90:711–716.

[36] Moradpour D, Altorfer J, Flury R, Greminger P, Meyenberger C, Jost R, et al. Chlorpromazine-induced vanishing bile duct syndrome leading to biliary cirrhosis. Hepatology 1994;20:1437–1441.

[37] Yeung E, Wong FS, Wanless IR, Shiota K, Guindi M, Joshi S, et al. Ramipril-associated hepatotoxicity. Arch Pathol Lab Med 2003;127:1493–1497.

[38] Mazeika PK, Ford MJ. Chronic active hepatitis associated with diclofenac sodium therapy. Br J Clin Pract 1989;43:125–126.

[39] Clarke AT, Mills PR. Atorvastatin associated liver disease. Dig Liver Dis 2006;38:772–777.

[40] Russo MW, Hoofnagle JH, Gu J, Fontana RJ, Barnhart H, Kleiner DE, et al. Spectrum of statin hepatotoxicity: experience of the drug-induced liver injury network. Hepatology 2014;60:679–686.

[41] Yao F, Behling CA, Saab S, Li S, Hart M, Lyche KD. Trimethoprim sulfamethoxazole-induced vanishing bile duct syndrome. Am J Gastroenterol 1997;92:167–169.

[42] Kowdley KV, Keeffe EB, Fawaz KA. Prolonged cholestasis due to trimethoprim sulfamethoxazole. Gastroenterology 1992;102:2148–2150.

[43] Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, et al. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology 2015;148 e7.

[44] Chatrenet P, Regimbeau C, Ramain JP, Penot J, Bruandet P. Chronic active cirrhogenic hepatitis induced by fenofibrate. Gastroenterol Clin Biol 1993;17:612–613.

[45] Ghabril M, Vuppalanchi R. Drug-induced nodular regenerative hyperplasia. Semin Liver Dis 2014;34:240–245.

[46] Anania FA, Rabin L. Terbinafine hepatotoxicity resulting in chronic biliary-ductopenia and portal fibrosis. Am J Med 2002;112:741–742.

[47] Gendre G, Buclin T, Morard I, Fontannaz J, Berney JL. Terbinafine induced hepatitis with persistent cholestasis. Rev Med Suisse 2008;4:736–739.