Research Article

JOURNAL OF HEPATOLOGY

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

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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

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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.

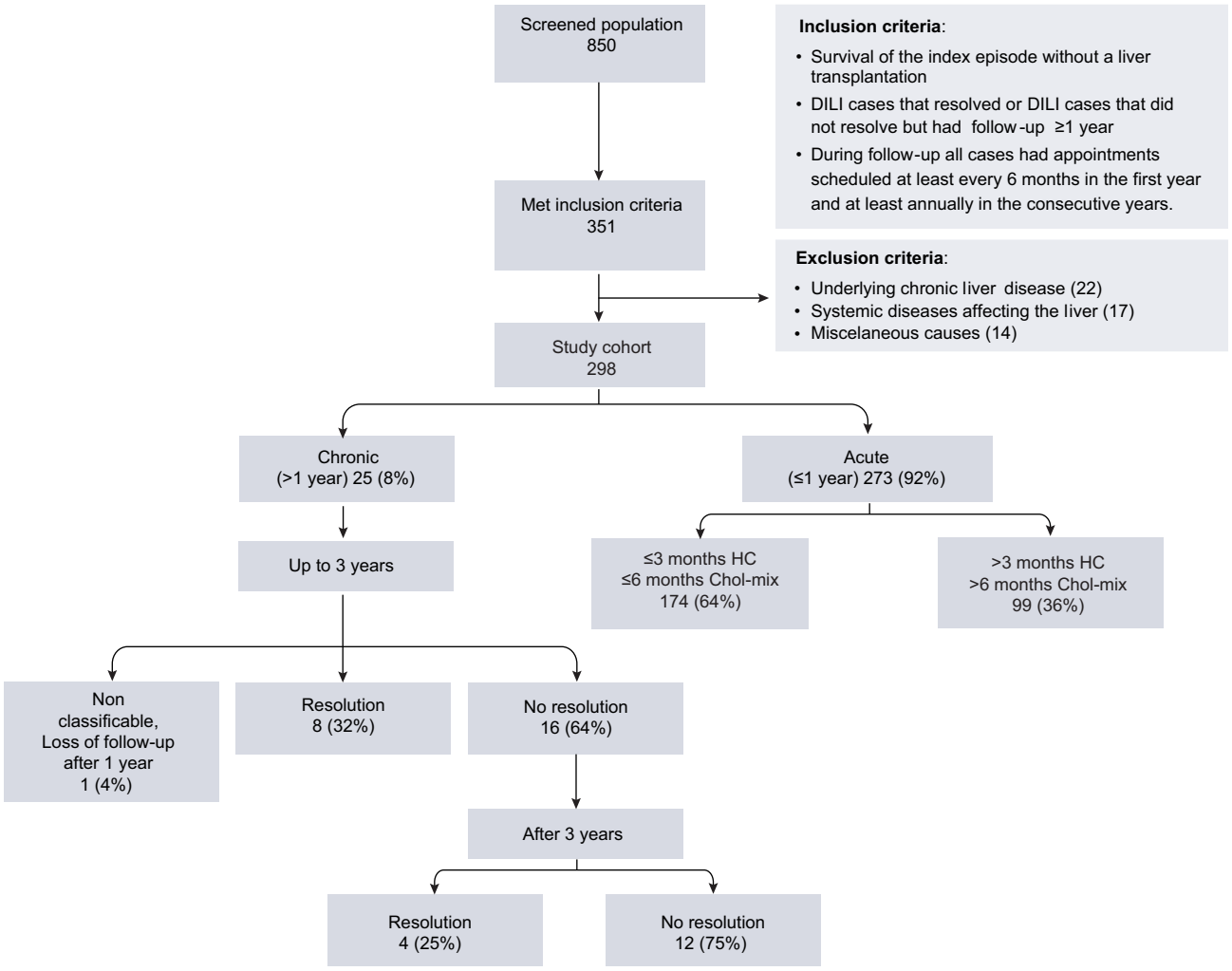

Fig. 1. Flow chart of the study cohort.

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