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Rechallenge in idiosyncratic drug-induced liver injury: An analysis of cases in two large prospective registries according to existing definitions

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ABSTRACT

Introduction: Data on positive rechallenge in idiosyncratic drug-induced liver injury (DILI) are scarce. We aim to analyse the clinical presentation, outcome and drugs associated with positive rechallenge in two DILI registries.
Methods: Cases from the Spanish and Latin American DILI registries were included. Demographics, clinical characteristics and outcome of cases with positive rechallenge according to CIOMS/RUCAM and *current* definitions were analysed.
Results: Of 1418 patients with idiosyncratic DILI, 58 cases had positive rechallenge (4.1%). Patients with positive rechallenge had shorter duration of therapy (p=0.001) and latency (p=0.003). In patients with rechallenge, aspartate transaminase levels were increased (p=0.026) and showed a prolonged time to recovery (p=0.020), albeit no differences were seen in terms of fatal outcomes. The main drug implicated in rechallenge was amoxicillin-clavulanate (17%). The majority of re-exposure events were unintentional (71%). Using both existing definitions of positive rechallenge, there were four cases which exclusively fulfilled the *current* criteria and five which only meet the *historical* definition. All cases of positive rechallenge, irrespective of the pattern of damage, fulfilled the criteria of either alanine transaminase (ALT) ≥3 times the upper limit of normal (ULN) and/or alkaline phosphatase (ALP) ≥2 times ULN.
Conclusions: Episodes of rechallenge were characterised by shorter duration of therapy and latency, and longer time to resolution, but did not show an increased incidence of fatal outcome. Based on our findings, ALT ≥3 times ULN and/or ALP ≥2 times ULN, regardless of the pattern of damage, is proposed as a new definition of rechallenge in DILI.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; ANA, antinuclear antibody; Anti-LKM, anti-liver-kidney microsomal antibody; AST, aspartate transaminase; ATC, Anatomical Therapeutic Chemical classification; CIOMS/RUCAM, Council for international organizations of medical sciences/Roussel Uclaf Causality Assessment Method; DILI, Drug-induced liver injury; DILIN, US Drug-Induced Liver Injury Network DILIN; FDA, Food and Drug Administration; HDS, herbal and dietary supplements; ICI, immune-checkpoint inhibitors; INR, international normalized ratio; IQR, interquartile range; LATINDILI, Latin American DILI network; RECAM, Revised Electronic Causality Assessment Method; SD, standard deviation; SMA, smooth muscle antibody; TBL, total bilirubin; ULN, upper limit of normal.

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1. Introduction

Idiosyncratic drug-induced liver injury (DILI) is an unexpected adverse reaction to the use of conventional drugs and herbal and dietary supplements (HDS) that represents one of the most frequent causes of drug withdrawal in preclinical and clinical phases [1]. Due to the variety in clinical presentation and the lack of specific biomarkers, diagnosis of DILI relies on the exclusion of other causes of liver damage [2].

In the context of this challenging diagnostic appraisal, positive rechallenge, defined as a reappearance of liver damage after administration (intentional or inadvertent) of a suspicious drug, represents strong evidence in favour of DILI. Indeed, causality assessment scales used to support the clinical judgement, such as the Roussel Uclaf Causality Assessment Method (RUCAM) endorsed by Council of International Organizations of Medical Sciences (CIOMS), or the more recently developed Revised Electronic Causality Assessment Method (RECAM), heavily score positive rechallenge [3,4].

Nonetheless, the decision of intentional re-exposure to the culprit drug has practical and ethical concerns [5], and is hardly justified unless the patient has shown benefits from taking the drug, there are no other options available, and data support that there is no potential risk of developing severe damage [6]. The Food and Drug Administration (FDA) guidelines recommends avoiding rechallenge in clinical trials in patients who have elevations of alanine aminotransferase (ALT) levels over 5-fold the upper limit of normal (ULN), or otherwise to do a closer follow-up and if they are re-exposed to the suspected drug [6].

Evidence about positive rechallenge after an episode of DILI is still scarce and its diagnosis has been based on biochemical criteria defined by expert opinion without strong scientific backing. In 1990, Benichou (on behalf of CIOMS/RUCAM) defined positive rechallenge as a raise of at least 2 times the baseline ALT levels in cases of hepatocellular liver injury, or an elevation of at least 2 times the baseline alkaline phosphatase (ALP) for cases who developed a cholestatic or mixed liver damage [7]. Further on, in 2017, this entity was defined by Hunt et al. as an increase of ALT levels 3–5 times (or greater) the ULN, irrespective of the pattern of damage [8].

One case series using a pharmaceutical safety database identified 88 cases of positive rechallenge after a possible hepatotoxic episode, of whom two progressed to acute liver failure and died [9]. On the other hand, in a recent retrospective multicentric study with a cohort of patients treated with immune-checkpoint inhibitors (ICI), 12 out of 51 (32.5%) had a positive rechallenge, although none of them evolved into a fatal outcome [10]. Likewise, in a multicentric prospective cohort of patients who had a severe immune-related hepatitis due to ICI, 35% had a positive rechallenge associated with mild-to-moderate severity [11]. Nevertheless, apart from immune-related hepatitis caused by checkpoint inhibitors, real-world data on the clinical features and prognosis of rechallenge in hepatotoxicity outside the framework of clinical trials are scarce.

Thus, in the present study, we aim to comprehensively describe the clinical characteristics and outcome of positive rechallenge after a first episode of DILI, and the causative drugs and clinical reason for re-exposure in a large series of patients from two prospective DILI registries. Likewise, we aim to propose an evidence-based definition that properly encompasses the cases of positive rechallenge.

2. Materials and methods

2.1. Study population

Information from well-characterized idiosyncratic DILI cases that were prospectively enrolled into the Spanish DILI registry (n=996) and the Latin American DILI (LATINDILI) Network (n=461) from the establishment of these registries to 2022 was retrieved. In-depth details of these registries have been described elsewhere [12,13]. For each DILI episode, a structured case report form was used to record clinical and pharmacological data, blood tests, imaging techniques to rule out other causes of liver disease, and the outcome of liver damage. Dose-related intrinsic DILI cases and second episodes of DILI caused by a different drug (recurrent DILI) were excluded. The study protocol was approved by local ethics committee, and all subjects gave their written informed consent.

The biochemical criteria for DILI were initially defined according to the criteria established by the CIOMS [3], and later adapted to those of Aithal *et al.* [14], i.e., serum ALT $\geq$5 times the ULN, ALP $\geq$2 times ULN, or ALT $\geq$3 times ULN together with total bilirubin (TBL) >2 times ULN. The causal relationship between the suspected culprit drug and liver injury was assessed by a panel three independent experts in DILI. Case likelihood categorization was then made based on traditional RUCAM categories [3].

The pattern of liver damage was classified using the nR value from the first available blood test after DILI recognition, i.e., (ALT or aspartate aminotransferase (AST), whichever highest/ULN)÷(ALP/ULN) [15]. Liver damage was classified as hepatocellular (nR $\geq$5), cholestatic (nR $\leq$2), or mixed (nR >2 and <5). Severity of liver injury was classified as mild (TBL <2 times ULN), moderate (TBL $\geq$2 times ULN), severe (TBL $\geq$2 times ULN, and either International Normalized Ratio, INR $\geq$1.5, ascites and/or encephalopathy, or another organ failure due to DILI), or fatal/transplantation (liver-related death or liver transplantation) [14].

Hypersensitivity was defined as positive if any of the following features were present at DILI recognition: fever, rash, serum eosinophilia, lymphopenia, or arthralgia. Eosinophilia was defined, based on blood work at DILI recognition, as serum eosinophils exceeding 4–6% of total leukocyte count depending on the normal range of individual hospitals, and lymphopenia as serum lymphocytes <10%. Cases with antinuclear antibody (ANA) $\geq$1:80, or smooth muscle antibody (SMA) or anti-liver-kidney microsomal antibody (anti-LKM) $\geq$1:40 were considered as cases with positive autoantibody titres.

Duration of treatment is the time (in days) elapsed from the start to the end of the therapy with the suspected drug responsible of DILI. Time to onset or latency is defined as days from the initial drug intake to the DILI diagnosis.

The suspected culprit drugs were classified according to the Anatomical Therapeutic Chemical classification (ATC) into anatomical pharmacological groups and subgroups.

2.2. Rechallenge

Rechallenge was defined as a re-exposition to the same causative agent responsible for a prior hepatotoxic episode. *Historical* positive rechallenge was defined as an increase of at least 2 times the baseline ALT levels in cases of hepatocellular liver injury, or an elevation of at least 2 times the baseline ALP for cases who developed a cholestatic or mixed liver damage [7]. On the other hand, *current* positive rechallenge was defined as an increase of ALT levels 3–5 times (or greater) the ULN, irrespective of the pattern of damage [8]. All positive rechallenge cases had some normal liver parameters, based on blood test, prior to liver damage after re-exposure. All rechallenge episodes analyzed in this study fulfilled at least one of the two existing definitions of positive rechallenge.

2.3. Statistical analysis

Demographic and clinical data for subjects included in this study were examined using descriptive statistics. For quantitative data, mean and standard deviation (SD), or median and interquartile range (IQR, i.e., the difference between the 25th and 75th percentiles) were calculated. Categorical data were presented using frequency distributions. Differences between groups, i.e., first episode of DILI and positive rechallenge, and *historical* and *current* definition, were tested with the Student's t test or Mann–Whitney U test, as appropriate, while qualitative variables were compared using the chi-squared test or Fisher's exact

test, as appropriate. Sensitivity analyses restricted to rechallenge cases with complete available information, and a comparison of characteristics between the first episode of DILI and positive rechallenge only in re-exposed patients, were conducted. Percentages were calculated based on available data, and no imputation methods were performed. All results were deemed statistically significant when a two-sided p-value was lower than 0.05. All analyses were performed using R version 4.1.3 (R Core Team 2022).

3. Results

A total of 1418 patients with well-vetted idiosyncratic DILI were included in the current study, including 965 from the Spanish DILI registry and 453 from the LATINDILI Network. Among them, 58 cases had a positive rechallenge (4.1%) (Supplementary Figure 1). Fifty-six patients had a single episode of positive rechallenge, while two patients were re-exposed twice to the same xenobiotic that resulted in two episodes of positive rechallenge in each patient. Detailed information of the individual cases with positive rechallenge is presented in Supplementary Table 1.

3.1. Comparison between first episode of DILI and positive rechallenge

Demographics, clinical characteristics, and laboratory findings of the first episode of DILI and positive rechallenge are shown in Table 1. There were no differences in age or sex distribution across groups. There were no differences in the pattern of liver injury, being the hepatocellular damage predominant in both groups (64% and 74% in the first episode and positive rechallenge, respectively; p=0.223). Of note, four cases exhibited a change in the pattern of liver injury between the first episode and the rechallenge. Three of them, two due to amoxicillin-clavulanate and the remaining one due to amiodarone, had a mixed liver injury in the first episode of DILI, whereas the type of liver injury in the positive rechallenge episode was hepatocellular. In addition, one case due to anti-tuberculosis drugs, presented with a cholestatic injury in the first episode, whereas he developed a hepatocellular injury after rechallenge.

When compared to cases with a first episode of DILI, those with positive rechallenge exhibited significantly shorter duration of treatment (median 31 vs. 15 days, respectively; p=0.001) and time to onset (median 27 vs. 15 days, respectively; p=0.003). Furthermore, a trend towards higher prevalence of positive autoantibodies in rechallenge compared with the first episode of DILI was seen (24% vs. 15%, respectively p=0.068). Moreover, patients with positive rechallenge showed marked elevations in AST levels compared to those with a first episode of DILI (median elevation of 11 and 6.3 times the ULN, respectively, p=0.026). Conversely, no differences were seen in other liver enzymes.

The majority of patients in both groups most commonly developed a moderate liver injury. Five patients (8.6%) with positive rechallenge developed a severe liver damage, and two patients (3.4%) evolved into a fatal injury. Among these latter cases, one who was re-exposed to amoxicillin-clavulanate successfully underwent a liver transplant, whilst the other one, who had a positive rechallenge to ibuprofen, got his condition progressively worsened and finally died. In addition, there was one elderly patient who had a positive rechallenge to amoxicillin-clavulanate and died due to non-liver-related causes.

We depicted the changes in DILI severity between the first episode and the positive rechallenge (Fig. 1). Most cases (61%) did not show a progression in the severity of liver damage in the rechallenge, or even in a small fraction of cases the damage was ameliorated in the rechallenge (16%). In contrast, 24% of patients exhibited an exacerbation in terms of liver injury severity. Over half of these latter cases progressed from a mild to moderate damage, and one case re-exposed to thiabendazole progressed from a mild damage in the first episode to a severe injury in the positive rechallenge. Furthermore, in one case re-exposed to amoxicillin-clavulanate the liver damage progressed from a moderate

Table 1
Demographics, clinical characteristics, laboratory parameters and outcome in the first episode and positive rechallenge in DILI cases from the Spanish and Latin American DILI registries.

	Whole registry (n=1418)	First episode of DILI (n=1360)	Positive rechallenge (n=58)	p value
Age (years), mean ±SD (range)	52±18 (11–91)	53±18 (11–91)	50±17 (23–90)	0.275
Female sex, n (%)	747 (53)	717 (53)	30 (52)	0.882
Body mass index (kg/m^2), mean±SD	26±4.4	26±4.5	25±4.2	0.320
Diabetes mellitus, n (%)	143 (10)	141 (11)	2 (3.4)	0.117
Dyslipidaemia, n (%)	153 (18)	148 (18)	5 (11)	0.213
Hypertension, n (%)	283 (20)	270 (20)	13 (22)	0.679
Underlying hepatic disease, n (%)	101 (12)	93 (12)	8 (18)	0.213
History of drug allergy, n (%)	79 (5.7)	76 (5.7)	3 (5.2)	1.000
Pattern of liver injury, n (%)				0.223
Hepatocellular	874 (64)	831 (64)	43 (74)	
Cholestatic	270 (20)	263 (20)	7 (12)	
Mixed	221 (16)	213 (16)	8 (14)	
DILI episode characteristics				
Jaundice, n (%)	904 (65)	868 (65)	36 (62)	0.662
Hospitalisation, n (%)	694 (50)	670 (50)	24 (41)	0.195
Hypersensitivity features, n (%)	554 (40)	532 (40)	22 (38)	0.780
Fever, n (%)	156 (11)	152 (11)	4 (6.9)	0.291
Rash, n (%)	126 (9.0)	122 (9.1)	4 (6.9)	0.814
Peripheral eosinophilia, n (%)	283 (20)	270 (20)	13 (22)	0.679
Lymphopenia, n (%)	209 (15)	199 (15)	10 (17)	0.621
Arthralgia, n (%)	46 (3.2)	42 (3.1)	4 (6.9)	0.120
Positive autoantibody titres, n (%)	218 (16)	204 (15)	14 (24)	0.068
Total oral daily nose (mg), median (IQR)	349 (75–1600)	300 (75–1650)	400 (100–1200)	0.677
Duration of therapy (d), median (IQR)	30 (9–72)	31 (10–74)	15 (5–40)	**0.001**
Time to onset (d), median (IQR)	26 (10–63)	27 (10–64)	15 (6–31)	**0.003**
Concomitant drugs, n (%)				0.998
None	454 (32)	436 (32)	18 (31)	
1–2 drugs	547 (39)	524 (39)	23 (40)	
3–4 drugs	268 (19)	257 (19)	11 (19)	
≥5 drugs	149 (11)	143 (11)	6 (10)	
Causality assessment, n (%)				**<0.001**
Possible	197 (16)	192 (17)	5 (8.6)	
Probable	699 (57)	678 (58)	21 (36)	
Highly probable	325 (27)	293 (25)	32 (55)	
Laboratory parameters at onset (x ULN), median (IQR)				
Total bilirubin	4.6 (1.1–9.9)	4.6 (1.1–10)	3.1 (1.2–6.8)	0.166
Aspartate aminotransferase (AST)	6.4 (3.0–19)	6.3 (2.9–18)	11 (4.5–22)	**0.026**
Alanine aminotransferase (ALT)	9.7 (4.8–23)	9.5 (4.8–22)	13 (5.1–28)	0.137
Alkaline phosphatase (ALP)	1.6 (1.0–2.6)	1.6 (1.0–2.6)	1.2 (0.8–2.0)	0.077
International Normalized Ratio (INR), median (IQR)	1.1 (1.0–1.3)	1.1 (1.0–1.3)	1.1 (1.1–1.2)	0.685

(continued on next page)

Table 1 (*continued*)

	Whole registry (n=1418)	First episode of DILI (n=1360)	Positive rechallenge (n=58)	p value
Creatinine (mg/dL), median (IQR)	0.9 (0.7–1.0)	0.9 (0.7–1.0)	0.9 (0.7–1.0)	0.594
Platelets (x10^3/μL), mean±SD	233±83	234±84	226±62	0.611
Severity, n (%)				0.705
Mild	448 (33)	427 (33)	21 (36)	
Moderate	778 (57)	748 (57)	30 (52)	
Severe	85 (6.2)	80 (6.1)	5 (8.6)	
Fatal/ transplantation	56 (4.1)	54 (4.1)	2 (3.4)	
Liver-related death, n (%)	32 (2.3)	31 (2.3)	1 (1.7)	1.000
Liver transplantation, n (%)	24 (1.7)	23 (1.7)	1 (1.7)	1.000
Death due to other causes[§], n (%)	20 (1.4)	19 (1.4)	1 (1.7)	0.575
Time to resolution (d), median (IQR)	94 (49–185)	94 (49–181)	152 (75–264)	**0.020**

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; INR, international normalised ratio; IQR, interquartile range; SD: standard deviation; ULN, upper limit of normal.

[§] During time of follow-up.

injury to a severe damage in the rechallenge, while in two cases who had had a moderate damage in the first episode their condition worsened to liver-related death or liver transplantation in the rechallenge.

In addition, patients who reported a positive rechallenge showed a prolonged time until biochemical resolution than those with a first episode of DILI (median 152 vs. 94 days; p=0.020).

In a sensitivity analysis restricted to rechallenge cases who, with the available information, fulfilled DILI criteria both in the first episode and the rechallenge (n=45), no substantial differences were observed. Indeed, the association between the prevalence of positive autoantibodies in the rechallenge is reinforced in this ancillary analysis (p=0.030) (Supplementary Table 2).

When we compared the characteristics of the first episode and positive rechallenge exclusively in re-exposed patients, the association between shorter treatment duration and time to onset in the rechallenge was consistent. In addition, nine patients developed lymphopenia in the rechallenge, while none of them had had lymphopenia in the first episode (p=0.022) (Supplementary Table 3).

3.2. Causative agents and causes of positive rechallenge

A total of 34 drugs were identified as causative agents of positive rechallenge in DILI cases. The most common drugs were amoxicillin-clavulanate (10 cases, 17%), followed by HDS (7 cases, 12%) and anti-tuberculosis drugs (combination of isoniazid, rifampicin and/or pyrazinamide) (4 cases, 6.9%) (Table 2). Thus, the most frequent ATC groups responsible for a positive rechallenge in DILI cases were anti-infectives for systemic use (n=18, 31%), cardiovascular system agents (n=8, 14%), musculo-skeletal system drugs and herbal and dietary supplements (n=7, 12% each) (Supplementary Table 4).

When separately analysing the distribution of causative agents responsible for the positive rechallenge in the two registries, amoxicillin-clavulanate was the main culprit drug in Spanish cases (22%), followed by HDS and anti-tuberculosis drugs (6.7%). On the other hand, HDS were the main causative agent involved in positive rechallenge among Latin American DILI cases, accounting for nearly one third of the positive rechallenge episodes (31%), followed diclofenac (15%) (Supplementary Table 5).

In an ancillary analysis, we examined the clinical characteristics of the first episode of DILI and positive rechallenge in the most frequent drugs (amoxicillin-clavulanate, HDS and anti-tuberculosis drugs) (Supplementary Table 6). Those cases with a positive rechallenge due to amoxicillin-clavulanate had higher total bilirubin levels in the rechallenge episode compared to the first episode of DILI (median 9.2 vs. 6.5 times ULN), and a worse prognosis of liver damage, with two cases presenting a severe injury (20%) and one patient who underwent a liver transplant (10%). In addition, time to biochemical resolution in rechallenge cases due to amoxicillin-clavulanate was significantly longer than in the first episode (p=0.001).

Reasons for drug re-exposure are presented in Table 3 and graphically depicted in Fig. 2. The most common cause was incidental re-

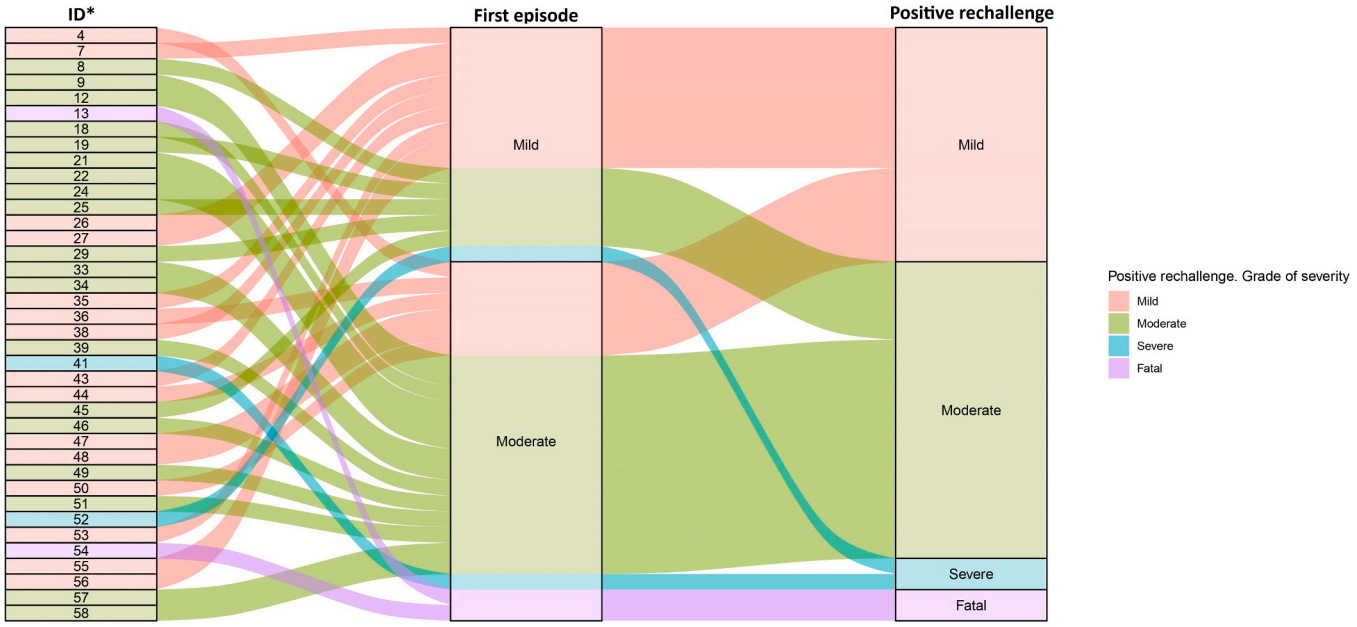

Fig. 1. Comparison of the grade of severity of liver damage in the first episode of DILI and positive rechallenge. * Detailed information of first episode of DILI and positive rechallenge according to the ID is available in Supplementary table 1.

Table 2
List of specific drugs responsible for the positive rechallenge in DILI cases in the Spanish and Latin American DILI registries.

Drug	Frequency, n (%)
Amoxicillin-clavulanate	10 (17)
Herbal and dietary supplements*	7 (12)
Anti-tuberculosis drugs†	4 (6.9)
Diclofenac	3 (5.2)
Amiodarone	2 (3.4)
Erythromycin	2 (3.4)
Ibuprofen	2 (3.4)
Methylprednisolone	2 (3.4)
Alfuzosin	1 (1.7)
Amoxicillin	1 (1.7)
Azathioprine	1 (1.7)
Azithromycin	1 (1.7)
Bosentan	1 (1.7)
Clomethiazole	1 (1.7)
Clopidogrel	1 (1.7)
Ebrotidine	1 (1.7)
Estradiol	1 (1.7)
Ezetimibe	1 (1.7)
Fenofibrate	1 (1.7)
Imipramine	1 (1.7)
Interferon α-2a	1 (1.7)
Interferon α-2b	1 (1.7)
Irbesartan	1 (1.7)
Ketoprofen	1 (1.7)
Leflunomide	1 (1.7)
Meloxicam	1 (1.7)
Mesalazine	1 (1.7)
Paroxetine	1 (1.7)
Propafenone	1 (1.7)
Sertraline	1 (1.7)
Simvastatin	1 (1.7)
Tiabendazole	1 (1.7)
Ticlopidine	1 (1.7)
Valproic acid	1 (1.7)

* Herbalife® products (3 cases), *Camellia sinensis* (2 cases), *Croton Cajuçara Benth* and *Peumus boldus* (1 case each).
† Combination of isoniazid, rifampicin and/or pyrazinamide.

Table 3
Causes of positive rechallenge in DILI cases in the Spanish and Latin American DILI registries.

Cause of drug re-exposure	Frequency, n (%)	Causative drugs
Incidental re-exposure	41 (71)	
Lack of diagnosis of first episode of DILI	28 (68)	Amoxicillin-clavulanate (n=7), ibuprofen (n=2), diclofenac (n=2), alfuzosin, amiodarone, amoxicillin, azithromycin, bosentan, clopidogrel, ebrotidine, erythromycin, fenofibrate, HDS*, irbesartan, ketoprofen, mesalazine, meloxicam, methylprednisolone, sertraline, simvastatin
History of DILI not reported in medical records, incorrect communication between physician and patient, change of prescribing physician between the first episode and the re-exposure	13 (32)	Amoxicillin-clavulanate (n=3), amiodarone, azathioprine, clomethiazole, erythromycin, ezetimibe, leflunomide, propafenone, tiabendazole, ticlopidine, valproic acid
Irreplaceable treatment	8 (14)	Anti-tuberculosis drugs (n=4), estradiol, methylprednisolone, interferon α-2[a], interferon α-2b
Self-medication (despite medical advice)	6 (10)	HDS (n=5)†, diclofenac
No prior data available	3 (5.2)	HDS‡, imipramine, paroxetine

* Camellia sinensis.
† Herbalife® products (n=3), *Camellia sinensis* (n=1), *Peumus boldus* (n=1).
‡ Croton Cajuçara Benth.

exposure (n=41, 71%). Within these cases, the vast majority (n=28) were re-exposed due to the lack of diagnosis of a first episode of DILI, while in 13 cases the reason of re-exposure was a non-reported history of DILI in the medical record, an incorrect communication between physician and patient (unclear explanation, lack of understanding by the patient), or change of prescribing physician between the first episode of DILI and the inadvertent re-exposure. Furthermore, eight cases were re-exposed due to the absence of alternative treatment for their condition (half of them were treated with anti-tuberculosis drugs). On the other hand, self-medication disregarding medical recommendations, mainly with HDS, accounted for the 10% of positive rechallenge episodes.

3.3. Comparison between historical and current definition of positive rechallenge

When we compared both existing definitions of positive rechallenge, i.e., *historical* and *current* definitions, no differences were seen neither in demographics, clinical presentation of the DILI episode, nor outcome between cases who fulfilled these criteria (Table 4). Notably, four cases re-exposed to erythromycin, amiodarone, estradiol and amoxicillin-clavulanate, all of them presenting a mixed pattern of liver damage, did not meet the *historical* criteria. On the other hand, five cases re-exposed to ticlopidine, azathioprine, meloxicam, amoxicillin-clavulanate and sertraline, did not meet the *current* criteria. All developed a cholestatic liver damage except the case with ticlopidine-related liver damage, which had mixed injury (Fig. 3).

As a consequence of the loss of some cases of positive rechallenge with both *current* and *historical* definitions, and in as much as pattern of liver damage may vary from the first to the second exposure (7% of positive rechallenge), we propose new criteria consisting of ALT $\geq$3 times ULN and/or ALP $\geq$2 times ULN, irrespective of the pattern of liver damage. Using this definition, the 45 re-exposed cases from the Spanish DILI registry would meet positive rechallenge criteria. Likewise, this definition has been internally validated with the 13 re-exposed cases from the LATINDILI Network, thus encompassing 100% of the positive rechallenge cases.

4. Discussion

This study has analysed the clinical characteristics and outcomes of the largest cohort of positive rechallenge in DILI cases enrolled in prospective Registries to date, outside the clinical trial setting. The liver damage appeared within a short duration of therapy and latency, and the cases had increased levels of AST at DILI recognition compared to the first episode. In addition, despite a similar severity of the DILI episode, the rechallenge event had a prolonged time to biochemical resolution of liver damage.

In these two long-term prospective registries, we found a positive rechallenge rate of 4.1%, slightly lower incidence than those reported in a retrospective single-center study in China, where the 7.3% of patients experienced a positive rechallenge [16]. These differences could be attributed to different prescription patterns. Indeed, in this latter study nearly 30% of DILI cases were due to herbal products, mainly Traditional Chinese Medicines, which in fact showed a higher incidence of rechallenge compared to cases treated with conventional medicines [16].

Most of these cases were inadvertently re-exposed to the culprit drug, which brings to light a plausible lack of awareness of patients about idiosyncratic hepatotoxicity. Most of these cases may had experienced a transient, mild episode of DILI that had resolved spontaneously, thus patients and physicians were unaware of the detrimental effects of a re-exposure to the same xenobiotic. Indeed, prior studies yielded that nearly 25% of patients were unaware of liver toxicity due to acetaminophen overdose [17], whereas patient or clinicians' awareness to idiosyncratic hepatotoxicity is yet a gap in knowledge to be addressed.

In addition, 13 cases of positive rechallenge were attributed to

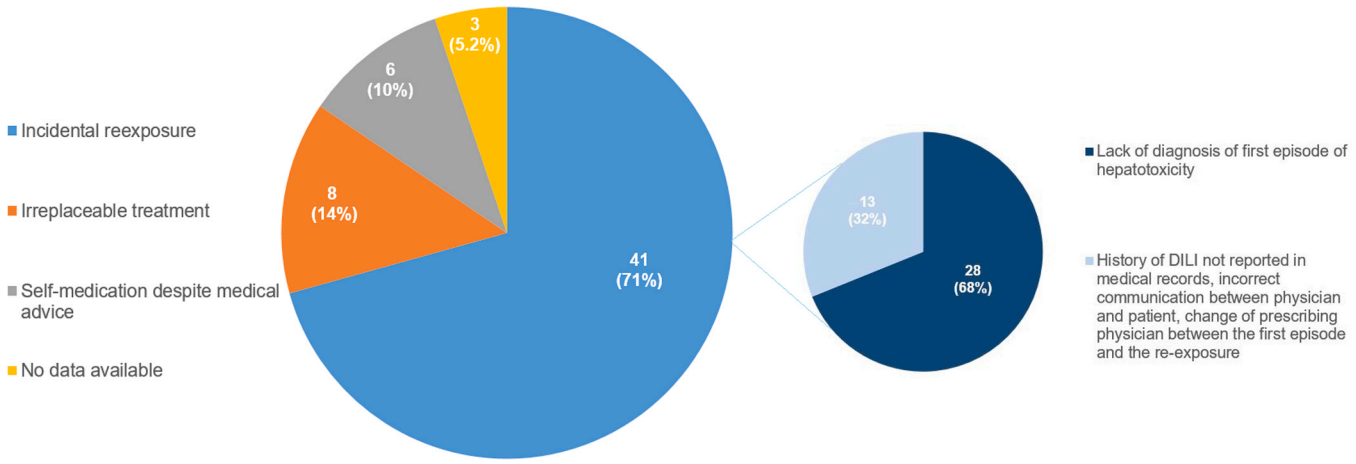

Fig. 2. Causes of drug re-exposure. No data were available in 3 cases (paroxetine, imipramine and *Croton Cajuçara Benth*).

failure to report the first episode of DILI in the medical record, or changes in the prescribing clinician between the two episodes. This series includes patients from Spain and Latin American countries (Argentina, Uruguay, Brazil and Paraguay), reflecting the variability in health care systems. Therefore, this issue calls in favour of the implementation of the electronic prescription and the development of artificial intelligence-based warning systems to address this type of re-exposures that are entirely preventable.

On the other hand, only 14% of cases were intentionally re-exposed to the same drug responsible for the first episode of DILI due to the lack of alternative therapeutic options. In our series, cases re-exposed to anti-tuberculosis treatment developed a mild liver damage. In a controlled trial in which patients who had had a first episode of DILI due to anti-tuberculosis drugs, treatment was re-administered in three different regimens. A 11% of patients developed a positive rechallenge, but none of them died, supporting the safety of reintroducing a potentially hepatotoxic anti-tuberculosis therapy [18]. Recent studies have shed light on the hepatotoxic potential of antituberculosis drugs, indicating that the pharmacogenetics of these drugs and their active metabolites seem to play a significant role in the pathophysiology of liver injury. Furthermore, these pharmacogenetic profiles could potentially serve as biomarkers worthy of consideration [19,20]. This pharmacogenetic influence is markedly affected by specific polymorphisms in the cytochrome P450 system. For instance, the concentration of isoniazid and its metabolite (acetylisoniazid) are NAT2 polymorphism-dependent [19]. These findings underscore the complexity of drug-induced hepatotoxicity and highlight the necessity for a deeper understanding of individual genetic predispositions in the context of antituberculosis therapy.

In addition, and although no cases of positive rechallenge due to the growingly used immune-checkpoints inhibitors were documented in our cohort, the clinical practice guidelines on management of toxicities from immunotherapy considers the intentional re-exposure to immune checkpoints inhibitors responsible for a prior mild or moderate liver injury after initial improvement with corticosteroid therapy, and always based on the individual risk-benefit balance, while permanent discontinuation of treatment should be considered in severe cases [21]. Furthermore, although more prolonged time to biochemical resolution was seen in those patients with positive rechallenge, no differences in liver-related death or liver transplantation rates were observed. These findings may support the idea of conducting carefully monitored re-exposures under specific situations with a strong clinical rationale, and in the absence of alternative therapeutic options [22]. A recently published Spanish study reported that anticancer drugs were the most commonly implicated pharmacological group in DILI cases (26%), surpassing anti-infectives (24%) [23]. This was a single-centre study, limited to a five-year period from 2018 to 2023, highlighting the increasing trend of immune checkpoint inhibitors topping the list of drugs causing DILI [23]. In addition to the overrepresentation of anticancer agents in this study compared with our series, it is possible that the reintroduction of immunotherapeutic agents previously implicated in liver injury under corticosteroid immunosuppression may confound rechallenge.

The most frequent drugs associated with positive rechallenge in our cohort was amoxicillin-clavulanate (17%), followed by herbal and dietary supplements (12%), and anti-tuberculosis drugs (6.9%). Firstly, given the well-known hepatotoxic potential of amoxicillin-clavulanate [24–26], it is likely that these cases were accidentally re-exposed without knowing that they had a first episode of DILI. This issue underlines the importance of conducting a thoughtful enquiry of previous exposures, and if appropriate, to record any suspicion of hepatotoxicity event, which may has gone underreported, following the recommendations in clinical practice guidelines [2,27,28].

Moreover, HDS were, overall, the second most frequent causative agents, and accounted for nearly one third of Latin American positive rechallenge cases. Notably, most of these cases were due to self-consumption without medical prescription. This fact, along with the misleading albeit widespread idea that these compounds are harmless, calls for educational campaigns warning about the detrimental effects of these products and the importance of avoiding self-medication without medical monitoring.

The role played by the innate and adaptive immune system in the development of DILI has been previously described [1,29]. In addition, an immune memory mechanism hypothesis has been proposed in those patients with a positive rechallenge. Thus, memory immune cells are already primed to specific antigens and therefore do not require a delay to generate an adaptive immune response, as it occurs in a first episode of DILI [30]. This hypothesis could explain why rechallenged patients had significantly shorter treatment duration and latency to DILI onset. The higher prevalence of positive autoantibodies in rechallenge episode compared to the first episode of DILI, could also be explained by this hypothesis. In fact, in a previous study of the cases of recurrent DILI (caused by another drug) collected in the Spanish Registry we also found that second episodes of DILI were more likely to be associated with features of autoimmune hepatitis [31].

Nevertheless, this immune predisposition does not always mean that the second exposure will lead to a more severe injury, especially in those cases who had a milder first episode of DILI, therefore suggesting the existence of an adaptive capacity of hepatocytes and the immune system [29]. Indeed, in most patients the rechallenge episodes was not associated with a worsened condition. A clinical trial with tolvaptan documented transient transaminase elevations following reinstatement of the agent in a previous DILI case, with the liver profile normalising over

Table 4
Comparison of demographics, clinical characteristics, laboratory parameters and outcome in DILI cases with positive rechallenge according to the historic and current definition.

	Historical definition (n=54)	*Current* definition (n=53)	p value
Age (years), mean±SD	49±17	48±16	0.629
Female sex, n (%)	29 (54)	27 (51)	0.775
Body mass index (kg/m^2), mean ±SD	25±4.3	25±3.9	0.786
Diabetes mellitus, n (%)	2 (3.7)	2 (3.8)	1.000
Dyslipidaemia, n (%)	5 (12)	5 (13)	1.000
Hypertension, n (%)	11 (20)	10 (19)	0.845
Underlying hepatic disease, n (%)	7 (17)	8 (20)	0.735
History of drug allergy, n (%)	3 (5.6)	3 (5.7)	1.000
Pattern of liver injury, n (%)			0.349
Hepatocellular	43 (80)	43 (81)	
Cholestatic	7 (13)	3 (5.7)	
Mixed	4 (7.4)	7 (13)	
DILI episode characteristics			
Jaundice, n (%)	35 (65)	31 (58)	0.501
Hospitalisation, n (%)	22 (41)	22 (42)	0.936
Hypersensitivity features, n (%)	21 (39)	19 (36)	0.745
Fever, n (%)	4 (7.4)	3 (5.7)	1.000
Rash, n (%)	4 (7.4)	3 (5.7)	1.000
Peripheral eosinophilia, n (%)	13 (24)	11 (21)	0.681
Lymphopenia, n (%)	9 (17)	8 (15)	0.824
Arthralgia, n (%)	4 (7.4)	3 (5.7)	1.000
Positive autoantibody titres, n (%)	13 (24)	14 (26)	0.780
Total oral daily nose (mg), median (IQR)	384 (88−1350)	400 (100−1200)	0.922
Duration of therapy (d), median (IQR)	15 (5−34)	15 (5−45)	0.957
Time to onset (d), median (IQR)	15 (6−31)	15 (6−36)	0.719
Concomitant drugs, n (%)			0.975
None	17 (31)	18 (34)	
1–2 drugs	22 (41)	19 (36)	
3–4 drugs	10 (19)	10 (19)	
≥5 drugs	5 (9.3)	6 (11)	
Laboratory parameters at onset (x ULN), median (IQR)			
Total bilirubin	3.1 (1.3–6.8)	2.5 (1.1–6.2)	0.555
Aspartate aminotransferase (AST)	11 (4.8–25)	11 (5.3–26)	0.875
Alanine aminotransferase (ALT)	15 (5.8–30)	15 (6.3–30)	0.713
Alkaline phosphatase (ALP)	1.2 (0.8–2.5)	1.1 (0.8–1.8)	0.629
Severity, n (%)			0.922
Mild	19 (35)	21 (40)	
Moderate	28 (52)	27 (51)	
Severe	5 (9.3)	3 (5.7)	
Fatal/transplantation	2 (3.7)	2 (3.8)	
Liver-related death, n (%)	1 (1.9)	1 (1.9)	1.000
Liver transplantation, n (%)	1 (1.9)	1 (1.9)	1.000
Death due to other causes[§], n (%)	1 (1.9)	1 (1.9)	1.000
Time to resolution (d), median (IQR)	152 (81−309)	152 (81−309)	0.994

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; IQR, interquartile range; SD: standard deviation; ULN, upper limit of normal.
[§] During time of follow-up.

time despite continued exposure to the offending agent, suggesting an adaptive liver response [32]. However, in our real-world cohort, the causative agent was always discontinued upon detection of liver injury. Nevertheless, in scenarios where the drug is considered essential, there is no viable therapeutic alternative, and the liver injury is mild, a wait-and-see approach may be warranted to ascertain whether it constitutes a rechallenge episode or an adaptive immune response. This approach need to be based on patient-centred decision-making, with an explanation of the risks and benefits, and the needs for close follow-up.

Our findings suggest an apparent drug-specific pattern in the presentation of positive rechallenge. Those cases re-exposed to amoxicillin-clavulanate tended to have higher total bilirubin levels and worse prognosis than in the first episode, whilst these findings were not seen in other cases re-exposed to HDS or anti-tuberculosis drugs. Nonetheless, the limited sample size of cases with positive rechallenge prevent to draw solid conclusions. This underscores the importance of generating evidence from prospective DILI registries, and the need of further investigations with larger cohorts of patients to validate these findings.

No differences between patients who fulfilled either the *historical* or *current* definitions of rechallenge were seen. Thus, altogether, both definitions seem to be useful to define positive rechallenge [7,8]. Nonetheless, it should be noted that cases who develop a mixed damage seem to be better defined according to *current* criteria, while cases with a cholestatic damage apparently fulfilled better the *historical* criteria. To a certain extent this might be forecastable, as the definition of *historical* criteria take into account the levels of ALP, whereas in *current* criteria only the level of ALT is considered, perhaps because the authors focused in the clinical trial setting [8]. Notably, in four cases there was a change in the pattern of injury (from mixed to hepatocellular in three cases and from cholestatic to hepatocellular in one case) between the first and second DILI episodes. Since the pattern of damage may vary between successive exposures to the same agent, if we use the biochemical criteria of ALT ≥3 times ULN and/or ALP ≥2 times ULN, regardless of the pattern of damage, we will include our entire positive rechallenge cohort, without missing any cases. Therefore, these criteria would be the better option to define positive rechallenge cases, while this needs to be validated in other different cohorts with a larger sample size.

The main strength of the current study is the inclusion of patients from both the Spanish and Latin American DILI registries, which share a conscientious and well-established methodology. However, some limitations should be acknowledged. The lack of information on negative rechallenge in these registries precludes comparison of these cases with our cohort, which undoubtedly would provide further insight into the risk factors and mechanisms that underlie in the development of a positive rechallenge.

In conclusion, episodes of positive rechallenge are characterized by increased AST levels and shorter duration of therapy and latency. These cases had a prolonged time to biochemical resolution, but poor outcome rates (death or liver transplant) did not differ from those of first episode of DILI patients. Clinicians should be aware to prevent unintentional re-exposures in patients with asymptomatic hypertransaminasemia with unclear etiology. We propose ALT ≥ 3 times ULN and/or ALP ≥ 2 times ULN irrespective of the pattern of damage, as a new definition of positive rechallenge based on the findings of our cohorts and pending validation in an external cohort.

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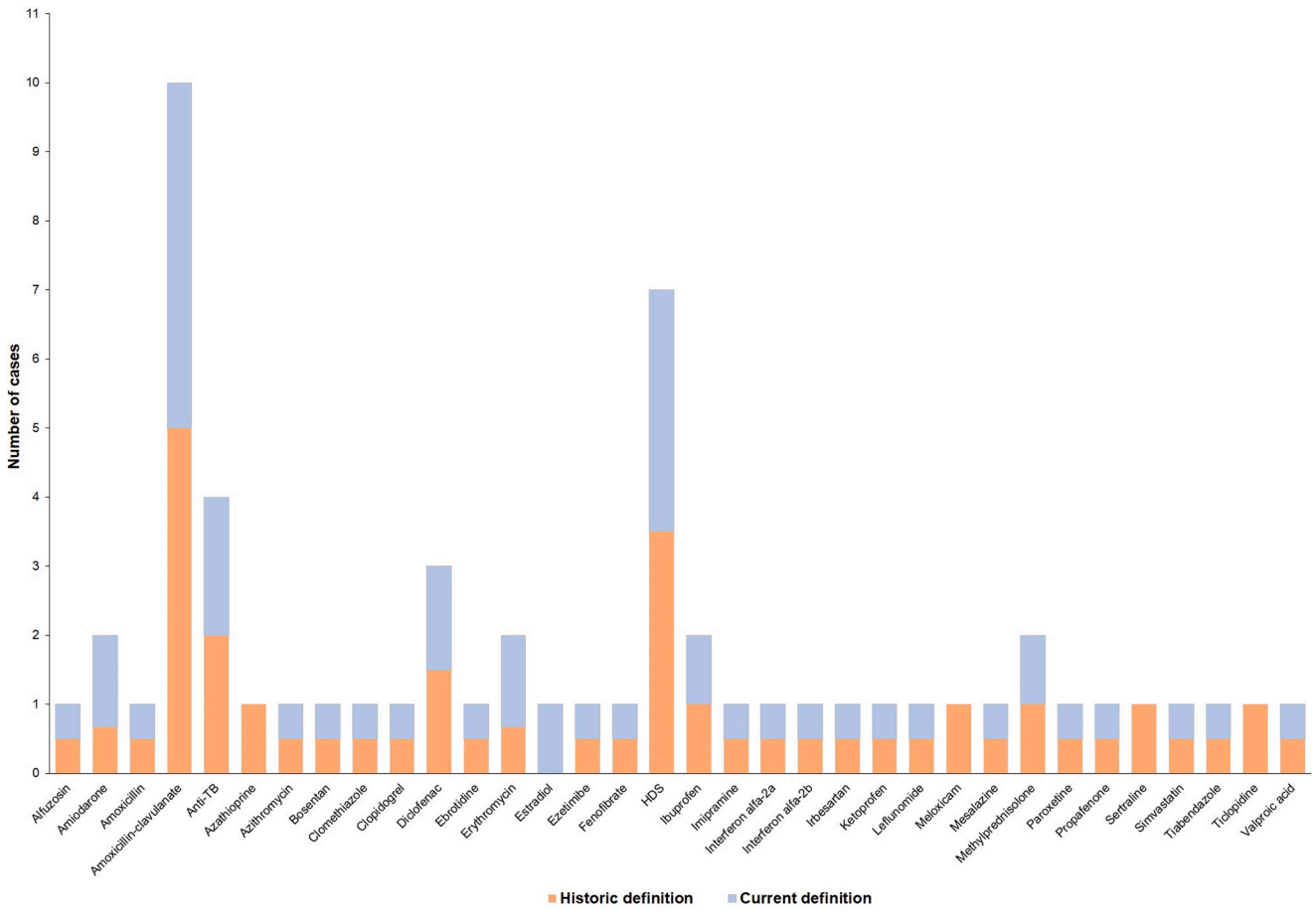

Fig. 3. Proportion of cases that fulfilled either the *historical* or *current* definition of positive rechallenge by causative drug.

editing, Supervision, Conceptualization. **Raúl J. Andrade:** Writing – review & editing, Supervision, Conceptualization. **Ismael Alvarez-Alvarez:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis. **Miren Garcia-Cortes:** Writing – review & editing, Supervision, Conceptualization. **Inmaculada Medina-Caliz:** Writing – review & editing, Resources. **Enrique del campo-Herrera:** Writing – review & editing, Resources. **Aida Ortega-Alonso:** Writing – review & editing, Resources.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.phrs.2024.107183.

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