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Clinical presentation, causative drugs and outcome of patients with autoimmune features in two prospective DILI registries

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Abstract

Background & aims: Idiosyncratic drug-induced liver injury (DILI) with autoimmune features is a liver condition with laboratory and histological characteristics similar to those of idiopathic autoimmune hepatitis (AIH), which despite being increasingly reported, remains largely undefined. We aimed to describe in-depth the features of this entity in a large series of patients from two prospective DILI registries.

Abbreviations: AIH, idiopathic autoimmune hepatitis; ALP, alkaline phosphatase; ALT, alanine aminotransferase; ANA, anti-nuclear autoantibodies; ASMA, anti-smooth muscle autoantibodies; AST, aspartate aminotransferase; CIOMS, Council for International Organizations of Medical Sciences; DI-ALH, drug-induced autoimmune-like hepatitis; DILI, idiosyncratic drug-induced injury; DILIN, Drug-Induced Liver Injury Network; HLA, human leukocyte alleles; IAIHG, International Autoimmune Hepatitis Group; IgG, immunoglobulin G; IQR, interquartile range; IST, immunosuppressive treatment; LATINDILI, Latin American DILI; LKM1, liver kidney microsomal antibodies type 1; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; pIgG, polyreactive IgG; RUCAM, Roussel Uclaf Causality Assessment Method; SD, standard deviation; ULN, upper limit of normal.

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Methods: DILI cases with autoimmune features collected in the Spanish DILI Registry and the Latin American DILI Network were compared with DILI patients without autoimmune features and with an independent cohort of patients with AIH.

Results: Out of 1,426 patients with DILI, 33 cases with autoimmune features were identified. Female sex was more frequent in AIH patients than in the other groups ($p = .001$). DILI cases with autoimmune features had significantly longer time to onset ($p < .001$) and resolution time ($p = .004$) than those without autoimmune features. Interestingly, DILI patients with autoimmune features who relapsed exhibited significantly higher total bilirubin and transaminases at onset and absence of peripheral eosinophilia than those who did not relapse. The likelihood of relapse increased over time, from 17% at 6 months to 50% 4 years after biochemical normalization. Statins, nitrofurantoin and minocycline were the drugs most frequently associated with this phenotype.

Conclusions: DILI with autoimmune features shows different clinical features than DILI patients lacking characteristics of autoimmunity. Higher transaminases and total bilirubin values with no eosinophilia at presentation increase the likelihood of relapse in DILI with autoimmune features. As the tendency to relapse increases over time, these patients will require long-term follow-up.

KEYWORDS
autoimmune features, autoimmune hepatitis, drug-induced autoimmune-like hepatitis, drug-induced liver injury, hepatotoxicity

1 | INTRODUCTION

Idiopathic autoimmune hepatitis (AIH) is an inflammatory liver disease of unknown aetiology and pathogenesis, generally characterized by the presence of autoantibodies and hypergammaglobulinaemia. This disorder has female predominance and is responsive to immunosuppressive treatment (IST).[1,2] However, external factors, such as viruses, vaccines, drugs or herbal products, could be risk factors for autoimmune hepatitis.[3,4] Additionally, idiosyncratic drug-induced liver injury (DILI) associated with drugs such as minocycline, nitrofurantoin, α-methyldopa, interferon and infliximab often present with an autoimmune-like phenotype,[5–7] and second DILI episodes are more likely to be associated with autoimmune features.[8]

Due to the lack of pathognomonic features and the absence of specific diagnostic criteria, distinguishing between AIH and DILI with autoimmune features is a diagnostic dilemma, and no harmonized definition of this clinical pattern of DILI has been reached.[9] In a recently held expert opinion conference,[10] the term drug-induced autoimmune-like hepatitis (DI-ALH) was endorsed by experts in both DILI and AIH.

Cases of DILI with autoimmune features exhibit laboratory and/or histological features similar to those of AIH. However, whether other differences exist between these two entities is a matter of debate. Liver damage usually manifests within 3 months after exposure to the suspected culprit drug, although the latency period may be longer,[11] and usually resolves after discontinuation of the drug, spontaneously or with IST (corticosteroids and/or azathioprine), with an average resolution time that can last months.[5]

Keypoints

- Distinguishing drug-induced liver injury (DILI) with autoimmune features from idiopathic autoimmune hepatitis (AIH) is hindered by the lack of pathognomonic features and the absence of specific diagnostic criteria.
- This study, based on data from two prospective DILI registries with long-term follow-up, strengths the knowledge of DILI with autoimmune features as a distinct entity in which statins play an important role as causative agents.
- Despite the absence of relapse without immunosuppressive therapy in DILI with autoimmune features is the rule, there is a risk of relapse especially in patients without eosinophilia and very high levels of transaminases and total bilirubin values at presentation, which highlights the need of long-term follow-up.

In retrospective analysis, the percentage of patients in AIH registries estimated to actually be triggered by a drug was 9.2%, with no cases of cirrhosis.[6] On the other hand, the frequency of DILI patients with autoimmune features was estimated at 6.7% (88/1,322) in the US Drug-Induced Liver Injury Network (DILIN),[7] while similar frequencies were more recently found in the Prospective European DILI Registry (4.2%, 12/247).[12]

The aim of this study was to describe the clinical characteristics, causative drugs and outcome of DILI patients with autoimmune features in a large series of patients collected in two prospective DILI registries.

2 | PATIENTS AND METHODS

2.1 | Study population

2.1.1 | Idiosyncratic drug-induced liver injury patients

Idiosyncratic DILI patients from the Spanish DILI Registry and the Latin American DILI (LATINDILI) Network since their establishment (1994 and 2011, respectively) until December 2021 were included in this study. In-depth details of these registries have been described elsewhere.[13,14] Study protocols were approved by the local ethics committees. All subjects gave written informed consent. Patients included were firstly evaluated by their clinician, and the case ascertainment was performed by an expert committee from the coordinating centre at the University of Malaga (Spain) based on the information collected in structured report forms. Other causes of liver disease were ruled out after an exhaustive evaluation.

The biochemical criteria for DILI cases were those proposed by the Council for International Organizations of Medical Sciences (CIOMS),[15] later adapted to those set in 2011.[16] The pattern of liver injury was defined by the R-value, that is, (alanine aminotransferase [ALT]/upper limit of normal [ULN])÷(alkaline phosphatase [ALP]/ULN). Cases were classified as hepatocellular ($R \geq 5$), cholestatic ($R \leq 2$) or mixed ($R > 2$ and $R < 5$). Severity was graded into mild, moderate, severe or fatal (death or liver transplantation).[16]

The causal relationship between the suspected culprit drug and liver injury was assessed by a panel of experts in DILI. Expert opinion was used to assess whether DILI consideration was reasonable and whether further data should be requested. Case likelihood categorization was then made based on traditional Roussel Uclaf Causality Assessment Method (RUCAM) categories. Only cases that scored at least 'possible' (≥3 points) were included.

2.1.2 | DILI patients with autoimmune features

Among DILI patients in the Spanish DILI Registry and the LATINDILI Network, cases were classified as having autoimmune features based on the following criteria: (1) fulfilling the biochemical criteria for DILI after ruling out alternative causes of liver disease, and having had exposure to a potentially hepatotoxic drug; (2) no underlying liver disease before taking the suspected drug; (3) intake of a drug prior to the onset of the liver damage. Also, they met two or three of the following: positive autoantibodies (anti-nuclear [ANA], anti-smooth muscle [ASMA] and/or anti-liver kidney microsomal type 1 [LKM1]), increased immunoglobulin G (IgG) levels above ULN or liver biopsy with features of AIH. Liver biopsy was considered suggestive if one of the following features was present: interface hepatitis, portal and periportal lymphoplasmacytic and eosinophilic infiltration and others similar to AIH. Patients with cirrhosis and autoimmune features were usually diagnosed as cases of autoimmune hepatitis, and therefore, these cases were not considered for inclusion in these prospective DILI registries. According to the American Clinical Practice Guidelines in Autoimmune Hepatitis, cirrhosis is rare in DILI with autoimmune features.[1] We have only considered this diagnosis in patients with cirrhosis who were on long-term treatment (≥9 months). In addition to RUCAM, the revised original score for AIH[17] was applied.

In these patients, *relapse* was defined as an increase in ALT or aspartate aminotransferase (AST) ≥2×ULN after biochemical remission without apparent cause.[18] Human leucocyte alleles (HLA) determination was at the discretion of each responsible physician to further assess the diagnosis.

2.1.3 | Patients with idiopathic autoimmune hepatitis

Between 2014 and 2015, patients with a diagnosis of AIH who were followed up in the hepatology unit of four Spanish hospitals were enrolled. Data used for comparisons with DILI with and without autoimmune features were those at AIH diagnosis, from cases with either an acute presentation of the condition or an asymptomatic phase with abnormal transaminases. These patients fulfilled the diagnostic criteria in the original scoring system of the International Autoimmune Hepatitis Group (IAIHG).[5] In these cases, the revised original score for AIH was applied.[17]

2.2 | Statistical analysis

Qualitative data were presented using frequency distributions, and differences were assessed with the chi-square test or Fisher's exact test, as appropriate. For quantitative data, mean and standard deviation (SD), or median and interquartile range (IQR) were computed, and the Student's *t*-test or Mann–Whitney U test, and the analysis of variance or the Kruskal–Wallis test, followed by post hoc analyses using Sidak or Dunn's test, as appropriate, were conducted. No imputation methods were performed to handle missing data. Analyses were performed using STATA version 17 (Stata Corporation). A two-sided *p*-value lower than 0.05 was considered statistically significant.

3 | RESULTS

Out of 1,426 DILI cases included in both registries, 33 DILI cases with autoimmune features (2.3%) were identified, of whom 23 were from the Spanish DILI Registry and 10 from the LATINDILI Network. A comprehensive clinical description of these cases is presented in Table S1.

3.1 | Characteristics of DILI with and without autoimmune features and AIH patients

Demographic, clinical characteristics and outcomes of the different patient groups were compared (Table 1). Twenty-nine DILI patients with autoimmune features met the above-mentioned autoimmune criteria, while four patients with missing information for IgG or liver biopsy were also included after a thoughtful evaluation of a panel of DILI and AIH experts based on the presence of relapse, score for AIH and suggestive HLA alleles. The female sex distribution showed significant differences ($p = .001$). Most patients with AIH were female (75%), compared to 58% and 53% of DILI patients with and without autoimmune features respectively. However, there were no differences in age ($p = .971$). The prevalence of both diabetes and hypertension was significantly higher in DILI patients either with and without autoimmune features than in AIH cases ($p = .022$ and $p = .031$, respectively), while the prevalence of dyslipidaemia was increased in DILI patients with autoimmune features compared to those without (24% vs. 11%, respectively; $p = .025$). In addition, males, but not females, who had DILI without autoimmune features had an increased body mass index compared to male who had DILI with autoimmune features (25.9 vs. 24.5, respectively; $p < .001$).

DILI with autoimmune features and AIH patients with an acute presentation had higher percentage of hepatocellular damage (84% and 81%, respectively) compared to 63% of DILI without autoimmune features ($p = .005$). On the other hand, the median duration of culprit therapy was significantly longer in DILI with autoimmune features (92 days) than in DILI without (29 days; $p < .001$).

The RUCAM classified 58% of DILI cases with autoimmune features as 'Probable' and 36% as 'Possible', while based on the revised original score for AIH, 58% of cases were classified as 'probable AIH' (10–15 points) and 39% were scored as 'definite AIH' (>15 points). Moreover, when applying this score to AIH cases, nearly half of them (44%) were classified as 'probable AIH', while 56% were scored as 'definite AIH'.

The values of ALT and AST were markedly increased in DILI patients with autoimmune features than in the other groups ($p < .001$). Furthermore, both DILI with and without autoimmune features showed higher total bilirubin levels than AIH patients.

IgG levels were raised in cases of DILI with autoimmune features (mean 23 g/L) and AIH (mean 21 g/L) compared with DILI without autoimmune features (mean 13 g/L) ($p < .001$). Furthermore, in DILI with autoimmune features and AIH patients, ANA and ASMA were the most frequent positive autoantibodies, with higher positive rates for ANA in DILI with autoimmune features, while AIH cases showed the highest rate in ASMA ($p < .001$). Notably, 79% of DILI with autoimmune features and 73% of AIH patients with positive ANA presented titres equal or over 1/160, while 64% of DILI with autoimmune features and 90% of AIH patients with positive ASMA had titres equal or over 1/80. Among 15 cases of DILI with autoimmune features in which HLA alleles were determined, 47% were positive for DR3 or DR4 alleles, while 78% of AIH cases were positive for these alleles.

There were no differences in severity of the episode between DILI cases with and without autoimmune features ($p = .203$). However, the median time to biochemical normalization was significantly longer in DILI with autoimmune features (162 days) than in DILI without (93 days; $p = .004$). Only the 6.9% of DILI patients without autoimmune features were treated with corticosteroids, while 63% of DILI patients with autoimmune features and 93% of AIH patients were treated with IST ($p < .001$), mainly with corticosteroids plus azathioprine. In addition, IST was significantly longer in DILI with autoimmune features (median 92 days) compared to DILI without autoimmune features (median 29 days, $p < .001$).

3.2 | Characteristics of DILI patients with autoimmune features according to the administered immunosuppression schedule

These patients were analysed according to the immunosuppression schedule, that is, no treatment during the episode, treatment from the onset and then withdrawn before an eventual relapse and treatment from the onset and maintained (Table 2).

No differences were seen in demographics, the prevalence of jaundice or hospitalization rate. However, DILI patients with autoimmune features with higher ALT values and a more severe injury were more likely to receive and maintain IST, compared with those with lower transaminases levels and milder liver damage. Nonetheless, the only patient who underwent an urgent liver transplant had not been previously treated with IST. Of nine DILI patients with autoimmune features who relapsed, four were on IST and discontinued or tapered it before the relapse, two were on IST at the time of relapse and three did not receive IST before relapse ($p = .491$).

3.3 | Characteristics of DILI patients with autoimmune features according to the presence of relapse

Characteristics of patients who had a relapse were compared with those who did not relapse (Table 3). Patients who relapsed were predominantly women (89%), compared to 50% of cases who did not relapse although the differences did not reach statistical significance ($p = .086$). Interestingly, six patients who did not experience a relapse had eosinophilia versus none of the patients who relapsed ($p = .048$).

Notably, patients who relapsed showed marked increases in median ALT, AST and total bilirubin levels compared to those who did not relapse ($p < .05$). In addition, patients who relapsed had a longer biochemical normalization time from the first episode than those who did not relapse (202 vs. 100 days, respectively; $p = .025$). A detailed clinical description of each case who relapsed is shown in Table S2. When comparing histological features, only focal necrosis showed a borderline significant difference between patients

who relapsed and those who did not (63% and 10%, respectively; $p = .043$) (Table S3).

During the follow-up of these patients, the likelihood of relapse increased over time. Thus, in the first 6 months after biochemical normalization, only 17% of patients relapsed, showing an upward trend throughout the years, reaching 50% after more than 4 years of follow-up. None of the relapses have any known specific trigger (viruses, drugs, vaccines or NAFLD/NASH). The median follow-up of patients who did not relapse was 1,050 days after onset and 720 days after liver parameters normalization (Figure 1).

TABLE 1 Demographics, clinical characteristics and outcome of cases with drug-induced liver injury with and without autoimmune features and idiopathic autoimmune hepatitis.

	DILI without autoimmune features ($n = 1,393$)	DILI with autoimmune features ($n = 33$)	AIH ($n = 71$)[a]	*p* value
Female sex, *n* (%)	732 (53)	19 (58)	53 (75)	.001
Age (years), mean ± SD (range)	52 ± 18 (11–91)	53 ± 20 (15–86)	53 ± 15 (17–80)	.971
Body mass index (kg/m^2), mean ± SD[b]				
Male	25.9 ± 4.0	24.5 ± 3.7	NA	<.001
Female	25.7 ± 4.8	25.3 ± 5.0	NA	.172
Diabetes, *n* (%)	142 (10)	3 (9.1)	1 (1.4)	.022
Hypertension, *n* (%)	278 (20)	10 (30)	7 (9.9)	.031
Dyslipidaemia, *n* (%)	152 (11)	8 (24)	NA	.025
Underlying hepatic disease, *n* (%)	98 (7.0)	2 (6.1)	NA	1.000
Other autoimmune comorbidities	NA	9 (27)	20 (28)	.924
Pattern of liver injury, *n* (%)				.005
Hepatocellular	818 (63)	26 (84)	35 (81)[c]	
Cholestatic	267 (21)	2 (6.5)	1 (2.3)	
Mixed	213 (16)	3 (9.7)	7 (16)	
Jaundice, *n* (%)	902 (66)	19 (58)	27 (41)	<.001
Hypersensitivity features, *n* (%)	554 (40)	10 (30)	NA	.272
Hospitalization, *n* (%)	692 (53)	12 (41)	NA	.208
Treatment duration (days), median (IQR)	29 (9–68)	92 (40–312)	NA	<.001
Time to onset (days), median (IQR)	25 (10–62)	94 (42–255)	NA	<.001
Liver profile at recognition (× ULN), median (IQR)				
Total bilirubin	4.6 (1.1–10)[f]	2.9 (1.5–6.6)[g]	1.1 (0.5–5.0)	<.001
Aspartate aminotransferase (AST)	6.2 (2.9–18)[e]	20 (11–29)[g]	9.7 (2.5–22)	<.001
Alanine aminotransferase (ALT)	9.2 (4.6–23)[e]	22 (13–34)[g]	9.2 (3.4–26)	<.001
Alkaline phosphatase (ALP)	1.6 (1.0–2.6)	1.8 (1.0–2.6)	1.3 (1.0–2.0)	.261
Immunoglobulin G (peak; g/L), mean ± SD	13 ± 7.0[e,f]	23 ± 11	21 ± 12	<.001
Positive autoantibodies titres, *n* (%)	252 (18)	33 (100)	65 (92)	<.001
ANA	164 (14)	30 (91)	55 (81)	<.001
ASMA	111 (10)	11 (34)	30 (70)	<.001
AMA	21 (2.0)	1 (3.1)	2 (2.8)	.466
Anti-LKM1	9 (1.1)	1 (4.0)	4 (19)	<.001
Immunosuppressive treatment, *n* (%)	69 (6.9)	21 (63)	66 (93)[d]	<.001
Corticosteroids only	69 (6.9)	5 (15)	26 (37)	
Corticosteroids and azathioprine	0 (0)	16 (48)	40 (56)	
Severity, *n* (%)				.203
Mild	443 (33)	14 (42)	NA	
Moderate	773 (57)	14 (42)	NA	
Severe	85 (6.3)	4 (12)	NA	
Fatal/liver transplantation	55 (4.1)	1 (3.0)	NA	

(Continues)

TABLE 1 (Continued)

	DILI without autoimmune features ($n=1,393$)	DILI with autoimmune features ($n=33$)	AIH ($n=71$)[a]	p value
Outcome				
Liver-related death, n (%)	33 (2.4)	0 (0)	NA	1.000
Liver transplant, n (%)	24 (1.7)	1 (3.0)	NA	.446
Normalization time (days), median (IQR)	93 (48–182)	162 (90–260)	NA	.004

Abbreviations: AIH, idiopathic autoimmune hepatitis; AMA, anti-mitochondrial antibodies; ANA, anti-nuclear antibodies; Anti-LKM1, anti-liver kidney-microsomal type 1 antibody; ASMA, anti-smooth muscle antibodies; DILI, drug-induced liver injury; IQR, interquartile range; SD, standard deviation; ULN, upper limit of normal.

[a]Biochemical parameter values obtained at the closest time to diagnosis. Patients were recruited during either an acute presentation of the condition or an asymptomatic phase.

[b]Differences in body mass index were calculated using z tests on the equality of means.

[c]Considering only AIH patients with an acute presentation ($n=43$).

[d]Three patients were treated with ursodeoxycholic acid, and two patients refused to receive immunosuppressive treatment.

[e]Significant differences between cases of DILI without and with autoimmune features ($p<.05$).

[f]Significant differences between cases of DILI without autoimmune features and AIH ($p<.05$).

[g]Significant differences between cases of DILI with autoimmune features and AIH ($p<.05$).

3.4 | Liver histology

The most common histological features found in biopsies of DILI cases with autoimmune features ($n=23$) were lymphoplasmacytic and eosinophilic infiltrate (70%), interface hepatitis (61%) and inflammation (43%). The most common grades of fibrosis found in this group were F0 and F1 (26% and 30%, respectively), followed by F2 (17%) and F3 (8.7%). Similarly, in biopsies from AIH patients ($n=65$), lymphoplasmacytic and eosinophilic infiltrate and inflammation (both 91%) and interface hepatitis (62%) were the most common histological features. The most common fibrosis stages in this group were F1 (32%) and F2 and F3 (25% each). Notably, lymphoplasmacytic and eosinophilic infiltrate and inflammation were significantly more common in AIH cases ($p=.034$ and $p<.001$, respectively) (Table 4).

3.5 | Causative drugs

The most common culprit agents in DILI with autoimmune features were nitrofurantoin (15%; median dose 100 mg/day), minocycline and fluvastatin (12% each; median dose 200 and 80 mg/day, respectively). Nevertheless, the sum of all statins, that is, fluvastatin ($n=4$), atorvastatin ($n=2$), rosuvastatin ($n=1$) and simvastatin ($n=1$), showed that statins were the most frequent drug class in these patients (24%) (Figure 2). Among patients taking nitrofurantoin, 20% had a relapse, while the proportion of patients taking minocycline and fluvastatin who had a relapse was 25% and 75% respectively. Notably, amoxicillin–clavulanate (19%), the combination of antituberculosis drugs (isoniazid, rifampicin and pyrazinamide, 3.3%) and ibuprofen (2.7%) were the most common causative agents involved in DILI without autoimmune features. In addition, in patients with AIH, levothyroxine (13%; probably related to the autoimmune background of these patients), paracetamol (7%), omeprazole, ibuprofen, lorazepam (5.6%) and enalapril (4.2%) were the most common drugs taken at the time of diagnosis, and 7.0% were on statin treatment, in line with the high prescription rate of these drugs in the general population.

4 | DISCUSSION

A correct characterization of DILI patients with autoimmune features may influence the decision to start immunosuppressants in the acute phase and the need for maintenance therapy. This study describes the clinical presentation, pathological features and outcome of well-documented DILI patients with autoimmune features included in the Spanish DILI Registry and the LATINDILI Network.

Drugs frequently associated with this entity are α-methyldopa, nitrofurantoin, minocycline and infliximab.[1] In a recent analysis, other drugs reported to be associated with this phenotype were interferon, statins, adalimumab, methylprednisolone, imatinib and diclofenac.[19] In the present study, nearly 25% of cases were induced by statins, in line with a retrospective cohort study in which statins were also the culprit agent in 36% of DILI cases with autoimmune features.[20] It is worth noting that, in our cohort of patients with AIH, 7% of them were on statin treatment.

The proportion of DILI patients with autoimmune features in the Spanish DILI Registry and the LATINDILI Network was 2.3%, lower than previously reported in other DILI cohorts,[7,12] probably related to differences in the diagnostic criteria and study design. In addition, unlike other studies, the female sex was also significantly less represented in our cohort (58%) compared with other findings in retrospective analysis in an AIH registry (92%),[6] or the DILIN cohort (91%).[7] These discrepancies might be related to the differences in the drugs causing liver injury, with nitrofurantoin and α-methyldopa (more often used in female patients) being more frequently reported as causative agents in other studies.[21,22]

TABLE 2 Characteristics of drug-induced liver injury with autoimmune features based on immunosuppression schedule.

	No IST during the first episode ($n=13$)[a]	IST from the onset and then withdrawn ($n=10$)	IST from the onset and maintained ($n=10$)	*p* value
Female sex, *n* (%)	8 (62)	5 (50)	6 (60)	.908
Age (years), mean ± SD (range)	60 ± 20 (19–86)	47 ± 19 (16–67)	49 ± 21 (15–75)	.226
Diabetes, *n* (%)	2 (15)	0 (0)	1 (10)	.762
Hypertension, *n* (%)	6 (46)	2 (20)	2 (20)	.437
Dyslipidaemia, *n* (%)	3 (23)	3 (30)	2 (20)	1.000
Underlying hepatic disease, *n* (%)	1 (7.7)	1 (10)	0 (0)	1.000
Other autoimmune comorbidities	2 (15)	2 (20)	5 (50)	.225
Pattern of liver injury, *n* (%)				.187
Hepatocellular	7 (64)	10 (100)	9 (90)	
Cholestatic	2 (18)	0 (0)	0 (0)	
Mixed	2 (18)	0 (0)	1 (10)	
Jaundice, *n* (%)	6 (46)	6 (60)	7 (70)	.559
Hypersensitivity features, *n* (%)	5 (39)	2 (20)	3 (30)	.733
Hospitalization, *n* (%)	3 (27)	3 (38)	6 (60)	.364
Treatment duration (days), median (IQR)	214 (77-314)[b]	113 (41-748)[d]	28 (6–56)	.015
Time to onset (days), median (IQR)	215 (67–313)	100 (41–749)	35 (12–105)	.054
Liver profile at DILI recognition (× ULN), median (IQR)				
Total bilirubin	1.5 (1.3–3.4)	4.4 (1.5–7.0)	3.2 (2.3–9.5)	.303
Aspartate aminotransferase (AST)	13 (10–22)	22 (13–30)	25 (20–29)	.249
Alanine aminotransferase (ALT)	13 (9.4–19)	28 (15–44)	29 (21–34)	.079
Alkaline phosphatase (ALP)	1.9 (1.0–2.6)	1.3 (0.9–2.1)	2.0 (1.3–2.2)	.487
Immunoglobulin G (peak value; g/L), mean ± SD	21 ± 12	19 ± 4.6	28 ± 14	.369
Positive autoantibodies titres, *n* (%)	13 (100)	10 (100)	10 (100)	–
ANA	13 (100)	9 (90)	8 (80)	.261
ASMA	4 (33)	3 (30)	4 (40)	1.000
AMA	0 (0)	0 (0)	1 (10)	.594
Anti-LKM1	0 (0)	1 (20)	0 (0)	.200
Suggestive DI-ALH biopsy, *n* (%)	8 (89)	7 (88)	6 (100)	1.000
Severity, *n* (%)				.047
Mild	9 (69)	3 (30)	2 (20)	
Moderate	3 (23)	6 (60)	5 (50)	
Severe	0 (0)	1 (10)	3 (30)	
Fatal/liver transplantation	1 (7.7)	0 (0)	0 (0)	
Outcome				
Resolved, *n* (%)	12 (92)	10 (100)	10 (100)	1.000
Liver transplant, *n* (%)	1 (7.7)	0 (0)	0 (0)	1.000
Liver-related death, *n* (%)	0 (0)	0 (0)	0 (0)	–
Normalization time (days), median (IQR)	127 (95–204)	136 (76–250)	193 (109–399)	.479
Relapse, *n* (%)	3 (25)	4 (40)	2 (20)	.491
No relapse, *n* (%)	9 (75)	5 (50)	6 (60)	
Worsening, *n* (%)	0 (0)	1 (10)	2 (20)	

Abbreviations: AMA, anti-mitochondrial antibodies; ANA, anti-nuclear antibodies; Anti-LKM1, anti-liver kidney-microsomal type 1 antibody; ASMA, anti-smooth muscle antibodies; IQR, interquartile range; IST, immunosuppressive treatment; SD, standard deviation; ULN, upper limit of normal.

Worsening is defined as an elevation of alanine and/or aspartate aminotransferases less than two times the upper limit of normal after biochemical normalization.

[a]A patient who received ursodeoxycholic acid and another patient who was treated with immunosuppressants only after relapsing were classified in this group.

[b]Significant differences between patients no treated during the episode and those with IST from the onset and maintained ($p<.05$).

[c]Significant differences between patients no treated during the episode and IST from the onset and then withdrawn ($p<.05$).

[d]Significant differences between patients with IST from onset and maintained group and those with IS from the onset and then withdrawn ($p<.05$).

TABLE 3 Characteristics of cases with drug-induced liver injury with autoimmune features that did and did not relapse.

	No relapse[a] ($n=14$)	Relapse ($n=9$)	p value
Female sex, *n* (%)	7 (50)	8 (89)	.086
Age (years), mean ± SD (range)	59 ± 22 (16–86)	49 ± 15 (15–67)	.294
Diabetes, *n* (%)	1 (7.1)	0 (0)	1.000
Hypertension, *n* (%)	6 (43)	1 (11)	.176
Dyslipidaemia, *n* (%)	3 (21)	3 (33)	.643
Underlying hepatic disease, *n* (%)	1 (7.1)	0 (0)	1.000
Other autoimmune comorbidities	2 (14)	3 (33)	.343
Pattern of liver injury, *n* (%)			.735
Hepatocellular	9 (75)	8 (89)	
Cholestatic	2 (17)	0 (0)	
Mixed	1 (8.3)	1 (11)	
Jaundice, *n* (%)	6 (43)	6 (67)	.400
Hypersensitivity features, *n* (%)	6 (43)	1 (11)	.176
Eosinophilia, *n* (%)	6 (43)	0 (0)	.048
Hospitalization, *n* (%)	3 (25)	3 (38)	.642
Treatment duration (days), median (IQR)	205 (102–314)	77 (10–748)	.186
Time to onset (days), median (IQR)	175 (94–313)	69 (22–720)	.329
Liver profile at DILI recognition (× ULN), median (IQR)			
Total bilirubin	1.5 (1.1–3.0)	7 (3.6–9.5)	.008
Aspartate aminotransferase (AST)	13 (10–19)	29 (18–36)	.029
Alanine aminotransferase (ALT)	12 (10–19)	31 (28–40)	.038
Alkaline phosphatase (ALP)	1.6 (0.8–2.6)	1.9 (1.4–2.6)	.537
Immunoglobulin G (peak value; g/L), mean ± SD	21 ± 11	19 ± 5.6	.858
Positive autoantibodies titres, *n* (%)	14 (100)	9 (100)	–
ANA	14 (100)	8 (89)	.391
ASMA	3 (23)	4 (44)	.376
AMA	0 (0)	1 (11)	.409
Anti-LKM1	0 (0)	0 (0)	–
Suggestive DI-AILH biopsy, *n* (%)	10 (100)	6 (75)	.183
Severity, *n* (%)			.265
Mild	9 (64)	3 (33)	
Moderate	5 (36)	5 (56)	
Severe	0 (0)	1 (11)	
Fatal/liver transplantation	0 (0)	0 (0)	
Outcome			
Resolved, *n* (%)	14 (100)	9 (100)	–
Normalization time (days), median (IQR)	100 (90–202)	202 (176–395)	.025

Abbreviations: AMA, anti-mitochondrial antibodies; ANA, anti-nuclear antibodies; Anti-LKM1, anti-liver kidney-microsomal type 1 antibody; ASMA, anti-smooth muscle antibodies; IQR, interquartile range; SD, standard deviation; ULN, upper limit of normal.

[a]Patients who did not receive immunosuppressive treatment, or it was withdrawn before an eventual relapse. The patient who underwent liver transplantation was excluded from this analysis.

To differentiate the clinical presentation of DILI with autoimmune features from AIH is crucial. In our study, we have found that positivity rate for ASMA was higher in AIH cases than in DILI with autoimmune features. Conversely, in a proof-of-concept study, positive ASMA prevalence was similar between these groups, while IgG autoantibodies specific to centromere protein B, chromatin, mitochondrial antigen, myosin and nucleosome antigen seemed to better differentiate these two entities.[23] More recently, Taubert et al. found that polyreactive IgG (pIgG) was more accurate than classic autoantibodies for AIH diagnosis.[24] Therefore, the relevance of IgG autoantibodies signatures and pIgG, rather than classical antibodies, in the differential diagnosis of these entities must be assessed further in future studies.

Absence or minimal liver fibrosis has been described as a signature in DILI patients with autoimmune features. Two cases presented cirrhosis at the time of the DILI diagnosis, without having a prior diagnosis of chronic liver disease. One was under chronic intermittent treatment with nitrofurantoin due to recurrent urinary tract infections, while the other had long-term therapy with cyproterone acetate (11 months). Our findings suggest that the differentiation between DILI patients with autoimmune features and AIH can not only rely on pathological features, requiring its combination with clinical and laboratory findings.[25]

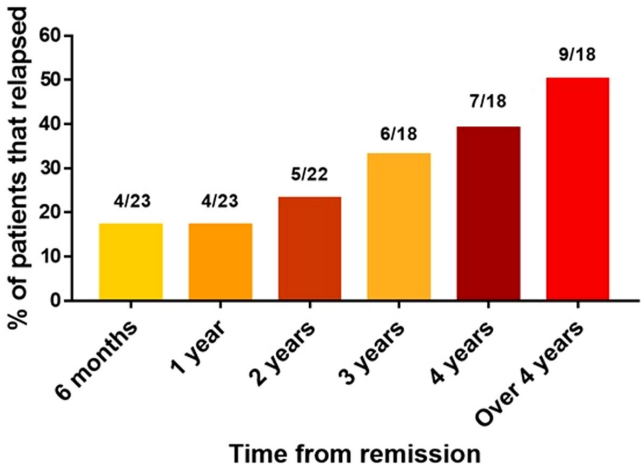

FIGURE 1 Relapse rate of cases with drug-induced liver injury with autoimmune features over time after remission. The cumulative prevalence of relapse was calculated considering the number of patients with available follow-up information at each time segment.

In line with other studies, the duration of the treatment with the causative drug was more prolonged in DILI patients with autoimmune features compared to DILI cases with the absence of autoimmune features. This fact could reflect an increased difficulty in diagnosing this phenotype of DILI, then taking more time until the discontinuation of the offending drug,[26] or, alternatively, may suggest that this autoimmune phenotype is induced after a longer exposure to a culprit agent.

DILI patients with autoimmune features received corticosteroids more frequently than DILI cases without, but less than patients with AIH. Of note, more than a third of DILI patients with autoimmune features did not require specific treatment owing to spontaneous biochemical normalization, similar to what has been previously reported.[26] However, in our series, the only patient who went into acute liver failure and needed urgent liver transplantation did not have time to receive immunosuppressants.

In our cohort of DILI patients with autoimmune features, we found an increase in relapse episodes over time, especially in those without peripheral eosinophilia and increased levels of transaminases and total bilirubin at onset, which highlights the need for long-term follow-up in this population. Relapse episodes in our cohort were not secondary to (any known) potential triggers such as drugs, toxins, vaccines or viruses. Interestingly, long-term exposure to statins, known for activating lupus erythematosus and other autoimmune disorders because of their immunomodulatory properties,[27] were more represented among those who relapsed, in line with other recently reported findings.[19]

Hypersensitivity signs were included as a feature of the so-called drug-induced AIH-like injury in the American Clinical Practice

TABLE 4 Histological features of cases with drug-induced liver injury with autoimmune features and idiopathic autoimmune hepatitis.

Histological features, *n* (%)	DILI with autoimmune features (*n* = 23)	AIH patients (*n* = 65)	*p* value
Lymphoplasmacytic and eosinophilic infiltrate	16 (70)	59 (91)	.034
Monocytic infiltrate	5 (22)	10 (15)	.525
Inflammation	10 (43)	59 (91)	<.001
Fibrosis stage			
F0	6 (26)	9 (14)	.205
F1	7 (30)	21 (32)	1.000
F2	4 (17)	16 (25)	.573
F2–F3	2 (8.7)	1 (1.5)	.166
F3	2 (8.7)	16 (25)	.138
F4	2 (8.7)[a]	2 (3.1)	.279
Interface hepatitis	14 (61)	40 (62)	1.000
Focal necrosis	6 (26)	30 (46)	.138
Rosettes	3 (13)	13 (20)	.546
Ballooned hepatocytes	2 (8.7)	3 (4.6)	.603

Abbreviations: AIH, idiopathic autoimmune hepatitis; DILI, drug-induced liver injury; F, fibrosis stage.

[a]One patient was under chronic treatment with nitrofurantoin due to recurrent urinary tract infections, and the other one had long-term therapy with cyproterone acetate (11 months).

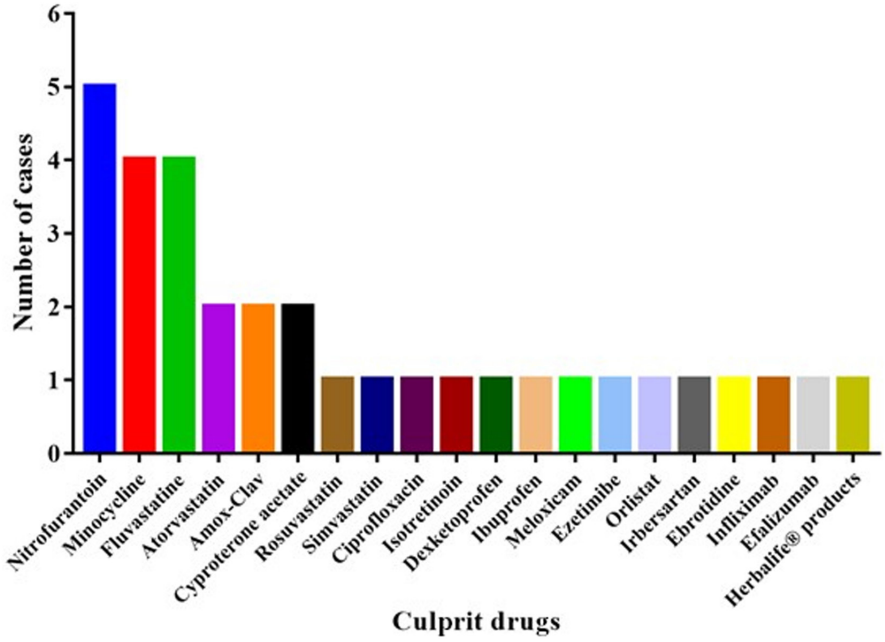

FIGURE 2 Most frequent culprit drugs in cases with drug-induced liver injury with autoimmune features.

Guidelines of AIH.[1] Remarkably, we found that eosinophilia was frequent in DILI patients with autoimmune features who did not relapse while absent in those who relapsed. Previous studies have associated eosinophilia with better outcomes of DILI.[28] Consistently, a genetic study from the Spanish DILI Registry showed that patients with serious DILI outcomes were carriers of low or intermediate IL-10-producing haplotype and had lower peripheral eosinophil counts.[29]

The absence of relapse after stopping IST has been previously proposed as a criterion of DI-ALH diagnosis.[6,26,30] However, these criteria preclude to make a diagnosis during the acute presentation, as a long-term follow-up of the patients is needed for ascertaining the absence of relapse. Although some of our cases had a relapse, none of them had evidence of underlying liver disease, all available previous liver tests before taking the suspected drug were normal, and all of them had a temporary relationship between the intake of the drug and the onset of the liver damage. Hence, a fundamental issue is as to whether these patients belong to the so-called DI-ALH entity. If so, DI-ALH could be classified based on the evolution of this condition as 'self-limited', where injury improves after discontinuation of the offending drug with or without an initial steroid treatment, or 'self-perpetuating', where the drug induces an autoimmune-like hepatitis which becomes chronic and needs immunosuppression maintenance. The self-perpetuating cases could indeed be true AIH, *unmasked* by the drug. Interestingly, in a Swedish DILI Registry and during a mean follow-up of 10 years, 23 of 685 patients (3.4%) had been hospitalized for liver disease, and AIH developed in 5/23 (22%) after a mean of 5.8 years, suggesting that a fraction of DILI cases triggering AIH may go unnoticed at presentation, or alternatively that persistent toxic liver injury might result in late AIH presentation.[31] Whether unmasking AIH is related to the severity of the liver injury and/or specific drugs more capable of triggering AIH by immunomodulatory effects is uncertain.

One of the main strengths of the present study is that DILI cases were prospectively collected and evaluated by a panel of experts. Therefore, these cases included in the Spanish DILI Registry and the LATINDILI Network do not have the bias of those identified *a posteriori* related to drugs on databases of AIH cases.[6,32] Nonetheless, some limitations should be acknowledged. The first is the small number of DILI patients with autoimmune features. In addition, the available follow-up data, although quite long, had an uneven temporality. In addition, cases of AIH used for comparison were collected retrospectively, and the histological assessment was not made by the same pathologist.

5 | CONCLUSIONS

In conclusion, this study adds to the knowledge of DILI with autoimmune features as a distinct entity in which certain drugs, such as statins, nitrofurantoin and minocycline, play a relevant role as causative agents. Furthermore, these patients are at risk of relapse and require long-term follow-up, especially in patients without eosinophilia and very high transaminase and total bilirubin levels at presentation. Further studies addressing the potential role of underlying comorbidities in susceptibility to presentation with this complex entity are warranted.

AUTHOR CONTRIBUTIONS

Miren García-Cortés, M. Isabel Lucena, Mercedes Robles-Díaz and Raúl J. Andrade were involved in study concept and design; Miren García-Cortés, Aida Ortega-Alonso, José Pinazo-Bandera, Agustín Castiella, Isabel Conde, Nelia Hernández, Martin Tagle, Raymundo Parana, Vinicius Nunes, Fernando Bessone, Elvira Bonilla-Toyos and Mercedes Robles-Díaz were involved in case recruitments; Miren García-Cortés, Aida Ortega-Alonso, Agustín Castiella, Nelia Hernández, Martin Tagle, Raymundo Parana, Vinicius Nunes, Fernando Bessone, M. Isabel Lucena, Mercedes Robles-Díaz and

Raúl J. Andrade were involved in case diagnosis; Gonzalo Matilla-Cabello and Ismael Alvarez-Alvarez were involved in statistical analyses; Miren García-Cortés, Aida Ortega-Alonso, Inmaculada Medina-Cáliz, Agustín Castiella, M. Isabel Lucena, Ismael Alvarez-Alvarez, Mercedes Robles-Díaz, Neil Kaplowitz and Raúl J. Andrade were involved in interpretation of data; Miren García-Cortés, Aida Ortega-Alonso, Gonzalo Matilla-Cabello, Inmaculada Medina-Cáliz, Ismael Alvarez-Alvarez and Mercedes Robles-Díaz were involved in drafting of the manuscript; Neil Kaplowitz, M. Isabel Lucena and Raúl J. Andrade were involved in critical revision of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors do not have any conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS APPROVAL STATEMENT

Study protocols were approved by the local ethics committees.

PATIENT CONSENT STATEMENT

All subjects gave written informed consent.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCE

Not applicable.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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