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ORIGINAL ARTICLE

Unveiling Drug-Induced Autoimmune-Like Hepatitis in Autoimmune Hepatitis Patients: A Multicenter Retrospective Study

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ABSTRACT

Background and Aims: Acute or chronic exposure to drugs or herbal and dietary supplements (HDS) can cause drug-induced autoimmune-like hepatitis (DI-ALH), a self-limiting condition resembling autoimmune hepatitis (AIH). We investigated the prevalence of drug exposure among AIH patients at diagnosis to recognise cases of DI-ALH and discern features predicting AIH development.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; ANA, antinuclear antibodies; anti-LKM1, anti-liver kidney microsome type1; anti-SLA, anti-soluble liver antigen; AST, aspartate aminotransferase; AZA, azathioprine; CBR, complete biochemical response; CNS, central nervous system; DI-ALH, drug-induced autoimmune hepatitis; DILI, drug induced liver injury; GGT, gamma glutamyl transferase; HDS, herbal and dietary supplements; i-AIH, idiopathic autoimmune hepatitis; IgG, immunoglobulin gamma; INR, international normalisednormalized ratio; mHAI, modified hepatic activity index; MMF, mycophenolate mofetil; PLTs, platelets; PRED, prednisolone; SMA, anti-smooth muscle antibodies.

Methods: We retrospectively included 705 patients diagnosed with AIH. DI-ALH was defined using published criteria. The clinical, biochemical, serological, and histological data of DI-ALH and AIH were analysed to identify predictors of the evolution of each phenotype.

Results: Most patients were female ($n = 496$, 70%), with a median age of 57 years and a median follow-up of 55 months. A 59% ($n = 417$) reported exposure to drugs or HDS, and 8% ($n = 58$) fulfilled the criteria for DI-ALH. Statins and HDS were the most common culprits. Patients with DI-ALH more frequently had acute severe or fulminant hepatitis (22% vs. 12%, $p = 0.013$) and higher transaminase levels (ALT: 966 vs. 591, $p = 0.001$) at diagnosis. In total, 97% of the patients received immunosuppression. DI-ALH patients had a faster biochemical response than i-AIH patients (4 vs. 5, $p = 0.031$), while treatment withdrawal was attempted in only 29% ($n = 17$). Approximately 30% ($n = 17$) of DI-ALH cases presented a flare during follow-up. Neither clinical, histological, nor serological findings nor RUCAM and RECAM could predict a DI-ALH flare.

Conclusions: DI-ALH is often under-recognised in clinical practice, leading to unnecessary long-term immunosuppression. A causal relationship between drugs and AIH, along with an attempt to withdraw treatment and long-term follow-up, is essential to prevent overtreatment-associated risks.

1 | Introduction

The term drug-induced autoimmune-like hepatitis (DI-ALH) was recently introduced by the International Autoimmune Hepatitis Group (IAIHG) and the Drug Herbal and Dietary Supplement-induced Liver Injury Consortium [1]. This term describes cases of drug-induced liver injury (DILI) that resemble autoimmune hepatitis (AIH), replacing the previously inconsistent nomenclature of DILI with autoimmune features [2–4]. DI-ALH specifically refers to acute liver injury associated with recent drug exposure, typically within 3 months although the time of exposure can be variable, characterised by the presence of circulating autoantibodies or elevated IgG levels and by histological findings consistent with AIH. In general, liver tests return to normal following discontinuation of the causative drug or, in some cases, after a short course of corticosteroids [1, 5].

Classic drugs associated with DI-ALH include α-methyldopa, nitrofurantoin, and minocycline [3, 6]. However, a growing number of drugs such as statins and infliximab have recently emerged as potential triggers [7]. Among herbal and dietary supplements (HDS), *Catha edulis*, *Tinospora cordifolia*, and turmeric have also been linked to DI-ALH [1]. Although DI-ALH is generally considered a self-limited condition, some cases progress to a perpetuating immune response, resulting in the need for long-term immunosuppression and developing the same characteristics as idiopathic AIH (i-AIH). Relapse rates are significant, with approximately 50% of patients with DI-ALH relapsing within 4 years of follow-up [7], and 22% of patients with drug-induced jaundice developing AIH over 6 years. Unfortunately, no clinical, biochemical, immunological, or histological markers have been identified to reliably predict the development of AIH and consequently guide treatment decisions and long-term management [8].

Despite its clinical significance, DI-ALH remains a rare type of DILI, accounting for only 2.3% of all DILI cases in Spanish and Latin DILI prospective registries [7]. Critical questions remain unanswered, such as the prevalence of DI-ALH among patients with AIH, the implicated causative agents, and the features predicting the development of AIH.

To address these gaps, we conducted a multicenter retrospective study in a large cohort of AIH patients to investigate: (1) the prevalence of drug exposure among AIH patients at diagnosis; (2) the number of cases related to drug exposure fulfilling the criteria for DI-ALH based on published definitions; and (3) the specific clinical, biochemical, immunological, and histological features of DI-ALH and AIH that predict the evolution of each phenotype.

2 | Material and Methods

2.1 | Study Design

This multicenter retrospective study included 705 patients diagnosed with AIH from 16 liver units in Spain (Figure S1). Patients were identified by revising the local databases of individuals with AIH. The inclusion criteria were as follows: (1) age ≥ 18 years at the time of AIH diagnosis; (2) probable or definite diagnosis of AIH according to the simplified criteria set by the IAIHG, as recommended by the guidelines of the European Association for the Study of the Liver (EASL) [9]; (3) liver biopsy at diagnosis with findings compatible with 'likely' or 'possible' AIH, according to the new consensus histology criteria from the International AIH pathology group [10]; (4) available data regarding drugs and HDS exposure at diagnosis; and (5) a minimum of 6 months follow-up after AIH diagnosis. The exclusion criteria were: (1) AIH variants (AIH/primary biliary cholangitis, AIH/primary sclerosing cholangitis or AIH/metabolic-associated steatotic liver disease, and AIH/viral hepatitis) and (2) pre-existing concomitant liver disease.

2.2 | Data Collection

Demographic (age and sex), clinical (date of AIH diagnosis, type of drug/supplement, time of exposure, date of treatment initiation, and type of treatment), biochemical (aspartate transaminase [AST], alanine transaminase [ALT], γ-glutamyltransferase [GGT], alkaline phosphatase [ALP], total bilirubin, IgG, and international normalised ratio [INR]), and serological (antinuclear antibodies [ANA], anti-smooth muscle antibodies [SMA], anti-liver kidney microsome type1 [anti-LKM-1], and anti-soluble liver antigen [anti-SLA]) data obtained at diagnosis and at 3, 6, and 12 months of follow-up were recorded. The last follow-up was considered the date of the last visit, death, or liver transplantation (LT).

Original reports of liver biopsies performed at diagnosis were retrospectively analysed. The modified hepatic activity index (mHAI) was used for the semi-quantitative assessment of the severity of inflammatory activity (degree of interface hepatitis, lobular inflammation and confluent necrosis) [10–12]. Mild inflammatory activity was defined as category A of the mHAI ≤ 1 and category B = 0 and category C ≤ 2. More than mild inflammation was defined as category A ≥ 2 and category B ≥ 1, or category C ≥ 3. Eosinophilic infiltration was assessed separately. Cirrhosis was defined as mHAI staging of5–6 or a METAVIR score of F4. Significant and advanced fibrosis were classified based on METAVIR scores of F2 and F3, respectively [13].

2.3 | Definitions

Among AIH patients, cases were classified as DI-ALH based on the following criteria: (1) fulfilment of the biochemical criteria for DILI proposed by the Council for International Organizations of Medical Sciences (CIOMS) and adapted in 2011 [14]; (2) exposure to a potentially hepatotoxic drug or HDS, defined as agents for which at least one case of hepatotoxicity has been reported, based on an in-depth review of the LiverTox database and relevant literature; (3) no evidence of underlying liver disease before taking the suspected drug; and (4) presence of autoimmune features (ANA, ASMA, and anti-LKM1 or anti-SLA) or IgG elevation, and (5) liver biopsy compatible with 'likely' or 'possible' AIH [10]. In contrast to the classical DILI definition, which limits drug exposure to within 3 months prior to liver injury, we extended the timeframe to 12 months to accommodate the variable latency observed in DI-ALH cases. Patients who did not fulfil these criteria were classified as having i-AIH. Patients with advanced fibrosis and/or cirrhosis were characterised as i-AIH, unless chronic exposure (≥ 9 months) to a hepatotoxic drug was confirmed [1, 5].

The pattern of liver injury was defined by the *R*-value. Cases were classified as hepatocellular ($R \geq 5$), cholestatic ($R \leq 2$), or mixed ($2 < R < 5$) [14, 15]. A panel of experts in AIH and DILI adjudicated the causal relationship between suspected culprit drug or HDS use and liver injury. Case likelihood categorisation was then made based on traditional Roussel Uclaf Causality Assessment Method (RUCAM) categories and the more recent causality assessment tool RECAM (an electronic updated version of RUCAM) [16, 17].

The severity of AIH at presentation was graded according to international guidelines as: (1) acute AIH, icteric without coagulopathy; (2) acute severe (AS), icteric with coagulopathy (INR ≥ 1.5); (3) acute liver failure (ALF), icteric with coagulopathy (INR ≥ 1.5) and overt hepatic encephalopathy (OHE); and (4) chronic AIH, cases that did not fulfil the previous criteria [18].

Patients were initially treated with corticosteroids (prednisolone [PRED] or budesonide) with or without azathioprine (AZA) or mycophenolate mofetil (MMF). Complete biochemical response (CBR) was defined as complete normalisation of transaminase and IgG levels at 6 and 12 months of follow-up according to the EASL guidelines. Disease flares were defined as an increase in AST or ALT $\geq 2\times$ the upper limit of normal (ULN) during tapering or after discontinuation of immunosuppression, after achieving CBR and without any apparent cause [19, 20]. Patients fulfilling the criteria for DI-ALH that presented with a flare during follow-up were considered to have developed an AIH phenotype.

2.4 | Ethics

The study was conducted in accordance with the Declaration of Helsinki and the protocol was approved by the Ethical Committee of the Hospital Clinic of Barcelona (HCB/2023/0343).

2.5 | Statistical Analysis

Statistical analyses were performed using the IBM SPSS Statistics 27. Continuous variables were expressed as median (interquartile range, IQR). The Mann–Whitney *U*-test was used to detect differences between independent samples. Categorical variables were presented using frequency distributions, absolute numbers, and percentages, where appropriate, and differences were assessed using the chi-squared test. To evaluate the performance of the RUCAM and RECAM scores, a receiver operating characteristic (ROC) curve was used to estimate the area under the curve (AUC), sensitivity, and specificity. The DeLong test using Med Calc Software was used to compare the AUCs. Two-sided *p*-values < 0.05 were considered statistically significant at a 95% confidence interval.

3 | Results

3.1 | Characteristics of AIH Patients at Diagnosis

The baseline characteristics of the patients included in the study are summarised in Table 1. Among the 705 patients analysed, 496 (70%) were female, with a median age of 57 years (IQR 44–67) at diagnosis and a median follow-up of 55 months (IQR 23–96). At presentation, 339 (48%) patients had acute AIH, 75 (11%) had AS, and 15 (2%) met ALF criteria. According to the mHAI, more than mild interface hepatitis and lobular inflammation were observed in 475 (67%) and 519 (74%) patients, respectively. Eosinophilic infiltration was detected in 358 patients (51%). Ninety-eight patients (14%) had cirrhosis at the time of diagnosis. Most patients tested positive for ANA ($n = 582$, 82%).

Six hundred eighty-six patients (97%) received immunosuppressive therapy. Most patients (86%) received PRED in combination with AZA, with a median treatment duration of 49 months (IQR 23–83). Sixty-two percent ($n = 439$) of the patients had CBR at 6 months of treatment. The median time to achieve CBR was 5 months (IQR 2–9). PRED was successfully discontinued in 64% ($n = 454$) of patients, while complete treatment withdrawal was attempted in 20% ($n = 137$) of patients. Nineteen (3%) patients did not receive immunosuppressive treatment; eight had a mHAI ≤ 4, five refused to be treated, four needed LT, and two died soon after diagnosis. At the last follow-up, 663 (94%) patients were alive, 23 (3%) died (48% from liver-related death), and 19 (3%) had undergone LT.

TABLE 1 | Characteristics of the patients included in the study.

Characteristics	All ($n=705$)	DI-ALH ($n=59$)	i-AIH ($n=646$)	p
Female sex (n, %)	496 (70%)	42 (71%)	454 (70%)	0.514
Age (years)	57 (44–67)	58 (51–66)	57 (44–67)	1.000
Follow-up (months)	55 (23–96)	47 (13–83)	57 (24–97)	**0.045**
Type of presentation (n, %)				
Chronic	276 (39%)	17 (29%)	259 (40%)	**0.013**
Acute	339 (48%)	29 (49%)	310 (48%)	
Acute severe	75 (11%)	9 (15%)	66 (10%)	
Acute liver failure	15 (2%)	4 (7%)	11 (2%)	
Biochemical parameters at diagnosis				
AST (U/L)	550 (152–1150)	809 (334–1402)	512 (145–1133)	**0.010**
ALT (U/L)	611 (210–1234)	966 (349–1728)	591 (198–1202)	**0.001**
GGT (U/L)	166 (79–308)	222 (115–325)	162 (77–308)	**0.036**
ALP (IU/L)	160 (108–255)	165 (129–247)	158 (106–259)	0.521
Bilirubin (mg/dL)	2.7 (0.9–9)	2.9 (1.1–9.0)	2.6 (0.9–9.0)	0.458
IgG (g/L)	18 (14–24)	17 (14–36)	1.9 (3–6)	0.105
INR	1.1 (1–1.3)	1.12 (1.02–1.49)	1.14 (1.02–1.3)	0.467
PLTs ($10^3\,\mu$L)	201 (157–250)	191 (162–240)	145 (157–250)	0.415
Histological findings				
mHAI grading	8 (5–10)	8 (5–10)	8 (5–10)	0.743
mHAI staging	1 (0–3)	1 (0–2)	1 (0–3)	0.983
Portal inflammation (n, %)	624 (86%)	54 (92%)	570 (91%)	0.215
Interface hepatitis[a] (n, %)	475 (67%)	37 (63%)	438 (70%)	0.236
Lobular inflammation[a] (n, %)	519 (74%)	41 (73%)	478 (76%)	0.624
Eosinophilic infiltration (n, %)	358 (51%)	34 (58%)	324 (50%)	0.280
Significant fibrosis ($\geq$ F2)	308 (44%)	15 (25%)	293 (45%)	**0.001**
Cirrhosis (n, %)	98 (14%)	1 (2%)	97 (15%)	**0.001**
Autoantibodies (n, %)	658 (93%)	51 (88%)	607 (94%)	0.090
ANA (n, %)	582 (82%)	43 (72%)	539 (83%)	0.062
SMA (n, %)	379 (54%)	25 (42%)	354 (55%)	0.133
SLA/LP (n, %)	26 (4%)	1 (2%)	25 (4%)	0.720
LKM (n, %)	13 (2%)	1 (2%)	12 (2%)	1.000
Treatment (n, %)	686 (97%)	57 (97%)	629 (97%)	1.000
PRED (n, %)	613 (89%)	51 (88%)	562 (87%)	0.841
PRED initial dose (mg/day)	50 (30–60)	50 (40–60)	50 (30–60)	0.739
Budesonide (n, %)	73 (11%)	6 (10%)	67 (10%)	0.392
Corticosteroids + AZA (n, %)	588 (86%)	44 (75%)	544 (84%)	1.000
Corticosteroids+ MMF (n, %)	35 (5%)	2 (3%)	33 (5%)	1.000
Duration of treatment (months)	49 (23–83)	28 (13–65)	50 (24–85)	**0.005**
Time to achieve CBR (months)	5 (2–9)	4 (2–6)	5 (2–9)	**0.031**
CBR at 6 months (n, %)	439 (62%)	36/47 (77%)	403/581 (69%)	0.327

(Continues)

TABLE 1 | (Continued)

Characteristics	All ($n=705$)	DI-ALH ($n=59$)	i-AIH ($n=646$)	p
CBR at 12 months (n, %)	469 (67%)	38/45 (84%)	431/555 (78%)	0.351
Corticosteroids withdrawal (n, %)	454 (64%)	38 (67%)	416 (64%)	1.000
Treatment withdrawal (n, %)	137 (20%)	17 (29%)	120 (18%)	0.058
Reinitiation of treatment (n, %)	50 (7%)	3 (18%)	47 (39%)	0.085
Biochemical parameters at 6 months				
AST (U/L)	32 (24–44)	26 (22–34)	32 (24–46)	**0.016**
ALT (U/L)	30 (20–47)	27 (18–38)	30 (21–47)	0.127
GGT (U/L)	34 (20–40)	31 (20–57)	35 (20–71)	0.460
ALP (IU/L)	78 (59–106)	70 (57–102)	79 (59–107)	0.232
Bilirubin (mg/dL)	0.8 (0.6–1.3)	0.8 (0.6–1)	0.8 (0.6–1.3)	0.387
IgG (g/L)	9 (8–13)	10 (6–12)	10 (6–13)	0.967
Biochemical parameters at 12 months				
AST (U/L)	28 (22–37)	25 (19–34)	28 (26–39)	**0.031**
ALT (U/L)	25 (17–37)	21 (16–32)	25 (19–49)	0.182
GGT (U/L)	27 (16–55)	23 (14–39)	27 (16–56)	0.144
ALP (IU/L)	78 (60–109)	74 (59–98)	96 (63–150)	0.424
Bilirubin (mg/dL)	0.8 (0.6–1.2)	0.7 (0.5–1.0)	0.7 (0.6–1.2)	0.185
IgG (g/L)	9 (6–12)	10 (7–12)	9 (6–13)	0.328
Outcome				
Alive (n, %)	663 (94%)	35 (93%)	608 (94%)	0.386
Death (n, %)	23 (3%)	1 (2%)	22 (3%)	
LT (n, %)	19 (3%)	3 (5%)	16 (3%)	

Note: Quantitative values are expressed as median (IQR). Bold is to highlight the statistically significant differences between groups.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; ANA, antinuclear antibodies; anti-LKM1, anti-liver kidney microsome type1; anti-SLA, anti-soluble liver antigen; AST, aspartate aminotransferase; AZA, azathioprine; CBR, complete biochemical response; DI-ALH, drug-induced autoimmune hepatitis; GGT, gamma glutamyl transferase; i-AIH, idiopathic autoimmune hepatitis; IgG, immunoglobulin gamma; INR, international normalised ratio; mHAI, modified hepatic activity index; MMF, mycophenolate mofetil; PLTs, platelets; PRED, prednisolone; SMA, anti-smooth muscle antibodies.
[a]The percentages refer to more than mild interface hepatitis and lobular inflammation according to the modified hepatic activity index.

3.2 | Frequency of Drug Exposure in Patients With AIH

At diagnosis, 417 (59%) patients were taking at least one chronic or short-term medication. The most commonly reported classes of agents were antihypertensive ($n=184$, 44%), central nervous system (CNS) ($n=106$, 25%), and lipid-lowering agents ($n=96$, 23%). Sixty-one (9%) patients were taking HDS, 58 (8%) were taking nonsteroidal anti-inflammatory drugs, and 39 (6%) were receiving antibiotics at the time of diagnosis (Figure 1). Fourteen patients received other drugs including α1-blockers ($n=8$), bisphosphonates ($n=4$), hydroxychloroquine ($n=4$), and antiretroviral treatment ($n=2$).

3.3 | DI-ALH Criteria at AIH Diagnosis

After detailed revision of the cases by the adjudication panel, 59 (8%) patients fulfilled the DI-ALH diagnostic criteria (Table 1). Most patients ($n=42$, 71%) were female, with a median age of 58 years (IQR 51–66). As shown in Figure 2, the most common culprit drugs were statins in 27% of the cases ($n=16$), followed by HDS in 14% ($n=8$). Classic drugs, such as nitrofurantoin and α-methyldopa, were implicated in only 3% of the cases ($n=2$). The mean duration of exposure to the implicated drug was 3 months (IQR 1–7).

According to the R-index, most cases presented with hepatocellular injury ($n=31$, 52%), followed by mixed ($n=21$, 36%), and cholestatic ($n=7$, 12%) injuries. While the RUCAM classified 66% ($n=39$) of DI-ALH cases as 'possible' and 34% ($n=20$) as 'probable', the RECAM score classified 31% ($n=18$) of DI-ALH as 'possible', 34% ($n=20$) as 'probable', and 12% ($n=7$) as 'highly probable'. All cases of DI-ALH were classified as probable or definite AIH, according to the simplified score.

Most patients ($n=57$, 97%) received immunosuppressive treatment. The median treatment duration was 28 months (IQR 13–65). An attempt to test for the normalisation of liver enzymes after discontinuation of the culprit drug was made in only half of the patients with DI-ALH ($n=30$, 51%). Immunosuppression was initiated directly in the remaining patients.

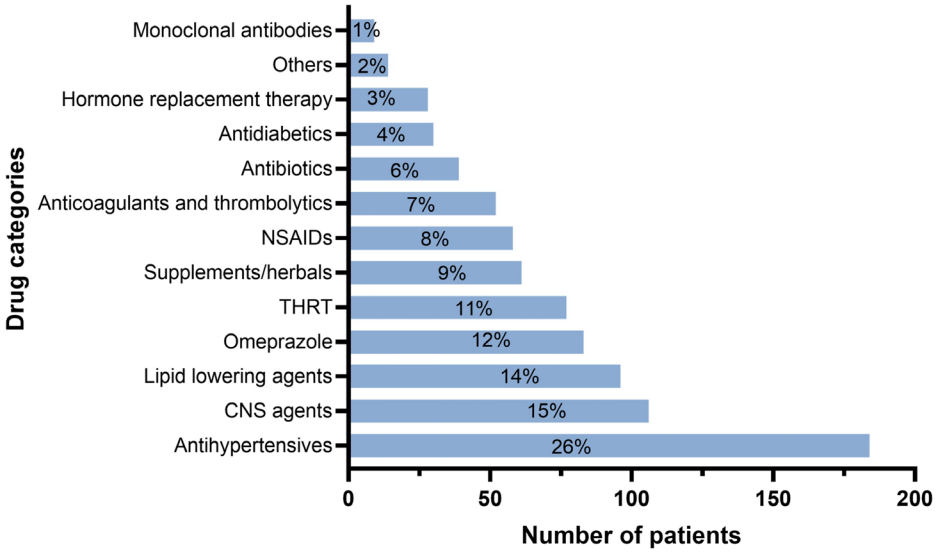

FIGURE 1 | Graphical representation of the drug categories exposure among AIH patients at the moment of disease diagnosis. More precisely, among antihypertensive agents, acetylcholine converting enzyme inhibitors/angiotensin receptor blockers accounted for 113 cases, b-blockers for 38 and diuretics for 33. Among CNS agents, 42 accounted for serotonin uptake inhibitors, 56 for benzodiazepines and 8 for antiepileptics. Among lipid-lowering agents, 91 cases accounted for statins with or without combination of ezetimibe and five cases accounted for fibrates. CNS, central nervous system; HDS, herbal or dietary supplements; NSAIDs, non-steroid anti-inflammatory drug; THRT, thyroid hormone replacement therapy.

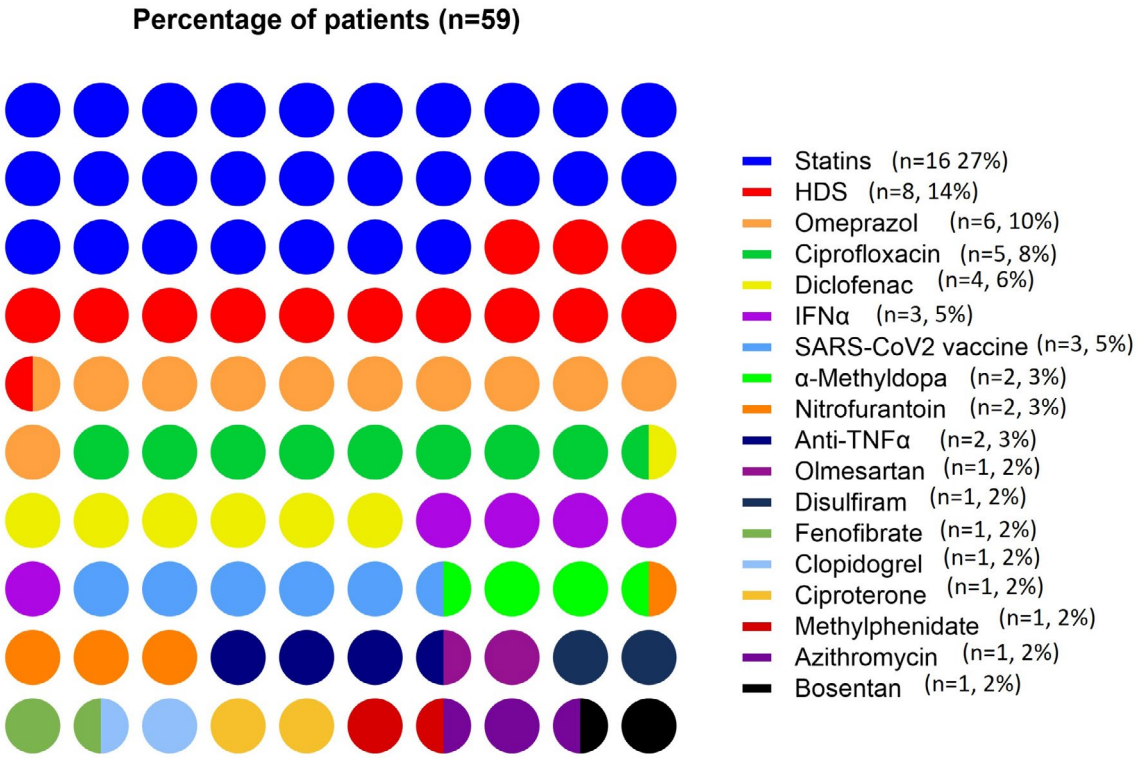

FIGURE 2 | Graphical representation of the culprit agents in cases classified as DI-ALH (each circle accounts for 1% of the patients). HDS, herbal or dietary supplements.

3.4 | Patients of DI-AILH Had Less Fibrosis at Diagnosis and Achieved the CBR Earlier Than Patients With i-AIH

A comparison of the characteristics of DI-ALH and i-AIH is presented in Table 1. Patients fulfilling the criteria for DI-ALH more frequently presented with AS hepatitis (15% vs. 10%) and ALF (7% vs. 2%) than with chronic AIH (29% vs. 40%), compared to patients classified as i-AIH ($p = 0.013$). Accordingly, patients with DI-ALH had higher AST (809 vs. 512, $p = 0.010$) and ALT (966 vs. 591, $p = 0.001$) levels at diagnosis, whereas no differences were observed in the levels of bilirubin and IgG.

Regarding liver histology, no differences in the presence of interface hepatitis, lobular inflammation, or eosinophilic infiltration were detected between the two groups. However, patients with i-AIH were more frequently diagnosed with significant fibrosis (≥F2) at diagnosis (45% vs. 15%, $p=0.001$) than patients classified as DI-ALH and had a higher percentage of established cirrhosis at initial presentation (15% vs. 2%, $p=0.001$). Notably, only one patient classified as having DI-ALH had established cirrhosis at diagnosis, which was attributed to chronic exposure (approximately 72 months) to methylphenidate.

Immunosuppressive treatment was initiated in almost all patients. No differences were observed in the type of immunosuppression or the initial PRED dose. Although the CBR rates at 6 and 12 months of treatment were comparable between the groups, the median time needed to achieve CBR was shorter for patients classified as DI-ALH than for those classified as i-AIH (4 vs. 5 months, $p=0.031$). Moreover, patients categorised as DI-ALH had lower AST levels than those with i-AIH at 6 (26 vs. 32, $p=0.023$) and 12 months (25 vs. 28, $p=0.029$) (Table 1). No other differences in biochemical parameters were observed. Corticosteroid withdrawal was achieved in 67% of patients with DI-ALH and 64% of patients with i-AIH. Complete treatment withdrawal was attempted in only a minority of patients (29% with DI-ALH and 18% with i-AIH). However, 18% of patients with DI-ALH and 39% of patients with i-AIH presented with flares after treatment discontinuation and had to restart immunosuppressive treatment.

Regarding the final outcome, the majority of patients were alive at the last follow-up. In the DI-ALH group, one patient died and three required LT directly at the time of diagnosis due to ALF. In contrast, in the i-AIH group, 22 patients died after a median time of 91 months (IQR 59–126) and 16 required LT after a median time of 42 months (16–139), in most cases due to advanced fibrosis at diagnosis or development of cirrhosis during follow-up.

3.5 | Evolution of Patients Classified as DI-ALH

Seventeen patients (29%) classified as having DI-ALH presented with a flare after a median time of 12 months (IQR 7–27). In 14 patients, flares were observed during the tapering of immunosuppression, in three patients after complete treatment withdrawal, while one patient who refused treatment presented a flare at 12 months of follow-up. Other causes of transaminase elevation were ruled out. Considering that a flare of the disease was associated with the perpetuation of the immune response and, consequently, with the development of an i-AIH phenotype, we searched for specific features that could predict the development of AIH.

In patients with DI-ALH, we did not observe significant differences in the clinical, biochemical, serological, or histological characteristics at diagnosis between those presenting with or without flares (Table 2). Regarding causative agents, a significant overlap was observed between the no-flare and flare cases, whereas the time of exposure to the culprit drug did not differ between the two groups. As shown in Figure 3, statins were the most frequent causative agents in both groups, followed by HDS, omeprazole, ciprofloxacin, and diclofenac. Among patients without flares, RUCAM classified 16 patients as 'highly probable/probable', and 26 patients as 'possible/unlikely'. According to the RECAM, 20 patients were classified as 'highly probable/probable' whereas 15 patients were classified as 'possible/unlikely' (for seven patients, the RECAM score could not be calculated due to insufficient data). We evaluated the discriminative capacity of RUCAM and RECAM for recognising DI-ALH without flares. Both RUCAM and RECAM demonstrated a low discriminating capacity for DI-ALH no-flare (RUCAM AUC 0.554, 95% CI 0.409–0.692, RECAM AUC 0.580, 95% CI 0.435–0.715; $p=0.749$) with a sensitivity of 76.4% and 58.8%, and a specificity of 38.1% and 57.1% for RUCAM and RECAM, respectively (Figure 3B).

3.6 | Characteristics and Evolution of Patients With Drug Exposure in the Absence of DI-ALH Criteria

Among patients characterised as i-AIH, 141 (20%) were receiving at least one drug or HDS that has been associated with acute or chronic liver injury but did not fulfil the criteria for DI-ALH. The median time of drug exposure was 25 months (IQR 4–42) and the most common agents were statins (43%), omeprazole (21%) and hormone replacement therapy (13%) (Figure S2). To clarify whether drug exposure, even in the absence of full DI-ALH criteria, still influences phenotype or treatment response, we compared patients with and without drug exposure at HAI diagnosis (Table S1). No significant differences were observed between the two groups concerning the type of disease presentation, biochemical and autoantibody profiles, treatment response, or final outcomes. Patients with drug exposure were older at presentation and more frequently exhibited portal inflammation on liver histology; however, no other histological differences were observed.

4 | Discussion

In this large, multicenter, retrospective analysis, we performed a thorough investigation of drug exposure in AIH, emphasising cases that fulfilled the diagnostic criteria for DI-ALH [1]. Our results revealed an 8% prevalence of DI-ALH among patients diagnosed with AIH, which was associated with the most frequently prescribed medication. Patients with DI-ALH lacked any specific features that can safely differentiate this entity from i-AIH and subsequently guide treatment decisions. Therefore, the diagnosis of DI-ALH was considered in only a minority of patients, leading to potential overexposure to unnecessary immunosuppressive treatment. However, almost 30% of patients who met the established criteria for DI-ALH [1] developed a 'classic' AIH phenotype requiring long-term immunosuppression.

Interestingly, a significant proportion of patients with AIH were exposed to at least one chronic or short-term medication at the time of disease diagnosis. The most frequently prescribed agents were among the most commonly administered medications, specifically antihypertensive, CNS, and lipid-lowering agents. Among patients with drug exposure, the prevalence of DI-ALH was 8%, which was higher than that recently reported

TABLE 2 | Comparison between DI-ALH patients presenting a flare versus no flare during tapering or after complete immunosuppression withdrawal.

Characteristics	No flare ($n=42$)	Flare ($n=17$)	p
Female sex (n, %)	29 (69%)	13 (77%)	0.753
Age (years)	58 (49–67)	57 (52–64)	0.980
Time of drug exposure (months)	3 (0.3–7)	3 (1–8)	0.568
Type of presentation (n, %)			
Chronic AIH	11 (26%)	6 (35%)	0.782
Acute AIH	20 (48%)	9 (53%)	
AS	8 (19%)	1 (6%)	
ALF	3 (7%)	1 (6%)	
Biochemical parameters at diagnosis			
AST (U/L)	1034 (372–1596)	752 (117–275)	0.844
ALT (U/L)	1085 (441–2100)	809 (381–1350)	0.451
GGT (U/L)	209 (98–311)	242 (168–412)	0.243
ALP (IU/L)	160 (115–202)	220 (145–291)	0.086
Bilirubin (mg/dL)	4 (1.05–12.4)	2.6 (1.1–4.8)	0.422
IgG (g/L)	16 (12–21)	20 (15–23)	0.069
INR	1.1 (1.0–1.6)	1.1 (1.1–1.4)	0.244
PLTs (10^3 μL)	179 (155–228)	233 (169–273)	0.054
Histological findings			
mHAI grading	8 (5–9)	9 (8–10)	0.072
mHAI staging	1 (0–2)	1 (0–2)	0.638
Portal inflammation (n, %)	39 (93%)	16 (94%)	1.000
Interface hepatitis[a] (n, %)	24 (57%)	13 (76%)	0.237
Lobular inflammation[a] (n, %)	29 (72%)	12 (71%)	1.000
Eosinophilic infiltration (n, %)	23 (55%)	11 (65%)	0.568
Significant fibrosis (≥ F2, Metavir)	12 (48%)	3 (18%)	0.557
Cirrhosis (n, %)	1 (2%)	0	1.000
Autoantibodies (n, %)	36 (86%)	16 (94%)	0.661
ANA (n, %)	19 (45%)	6 (35%)	0.578
SMA (n, %)	25 (43%)	354 (56%)	0.755
SLA/LP (n, %)	0	1 (6%)	0.288
LKM (n, %)	1 (2%)	0	1.000
Treatment (n, %)	41 (98%)	16 (94%)	0.497
PRED (n, %)	32 (76%%)	15 (88%)	1.000
PRED initial dose (mg/day)	60 (40–60)	40 (30–60)	1.000
Budesonide (n, %)	4 (9%)	1 (6%)	1.000
Corticosteroids + AZA (n, %)	28 (93%)	16 (100%)	0.536
Corticosteroids + MMF (n, %)	2 (7%)	0	0.420

(Continues)

TABLE 2 | (Continued)

Characteristics	No flare ($n=42$)	Flare ($n=17$)	p
Duration of treatment (months)	23 (11–55)	79 (27–106)	**0.039**
Time to achieve CBR (months)	3 (1–6)	5 (2–6)	0.267
CBR 6 months (n, %)	27/34 (79%)	9/13 (69%)	0.467
CBR 12 months (n, %)	29/32 (91%)	9/13 (69%)	0.168
Corticosteroids withdrawal (n, %)	31 (76%)	7 (44%)	**0.031**
Treatment withdrawal (n, %)	13 (32%)	4 (25%)	0.753
Biochemical parameters 3 months			
AST (U/L)	27 (21–37)	35 (28–58)	0.057
ALT (U/L)	29 (26–41)	63 (24–74)	0.155
GGT (U/L)	62 (30–126)	45 (36–81)	0.832
ALP (IU/L)	76 (55–89)	93 (71–119)	0.060
Bilirubin (mg/dL)	0.8 (0.6–1.0)	0.8 (0.6–1.4)	0.841
Biochemical parameters 6 months			
AST (U/L)	25 (22–34)	32 (24–63)	0.059
ALT (U/L)	23 (17–34)	30 (21–69)	0.126
GGT (U/L)	26 (16–48)	43 (31–128)	**0.014**
ALP (IU/L)	61 (55–83)	100 (71–143)	**0.001**
Bilirubin (mg/dL)	0.8 (0.7–1)	0.8 (0.5–1.3)	0.804
IgG (g/L)	10 (6–11)	12 (9–14)	0.358
Biochemical parameters 12 months			
AST (U/L)	23 (18–29)	29 (26–39)	**0.014**
ALT (U/L)	19 (14–29)	29 (19–49)	0.060
GGT (U/L)	22 (12–38)	23 (16–47)	0.299
ALP (IU/L)	70 (55–84)	96 (63–150)	**0.037**
Bilirubin (mg/dL)	0.8 (0.5–1.1)	0.7 (0.5–0.9)	0.320
IgG (g/L)	10 (7–12)	11 (8–15)	0.503
Outcome (n, %)			
Alive	38 (91%)	17 (100%)	**0.420**
Dead	1 (2%)	0	
LT	3 (7%)	0	

Note: Quantitative values are expressed median (IQR) where applicable. Bold is to highlight the statistically significant differences between groups.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; ANA, antinuclear antibodies; anti-LKM1, anti-liver kidney microsome type 1; anti-SLA, anti-soluble liver antigen; AST, aspartate aminotransferase; AZA, azathioprine; CBR, complete biochemical response; DI-ALH, drug-induced autoimmune hepatitis; GGT, gamma glutamyl transferase; i-AIH, idiopathic autoimmune hepatitis; IgG, immunoglobulin gamma; INR, international normalised ratio; mHAI, modified hepatic activity index; MMF, mycophenolate mofetil; PLTs, platelets; PRED, prednisolone; SMA, anti-smooth muscle antibodies.
[a]The percentages refer to more than mild interface hepatitis and lobular inflammation according to the modified hepatic activity index.

in prospective DILI registries (2.3%) [7]. This is in agreement with what has been previously reported for AIH, where the causative relationship with drug exposure was 9.2% [2]. This finding supports the fact that cases of DI-ALH are frequently misdiagnosed as AIH and are directly exposed to immunosuppressive treatment. Our findings further support this conclusion, as 97% of patients fulfilling the diagnostic criteria for DI-ALH received immunosuppression, with an attempt to wait for the normalisation of liver biochemistry after discontinuation of the culprit drug in only half of the patients. In addition, immunosuppression withdrawal was attempted in only a minority of cases (< 30%), suggesting that patients with DI-ALH may be unnecessarily exposed to long-term immunosuppression [21].

However, the absence of specific features makes the diagnosis of DI-ALH challenging in clinical practice. In addition,

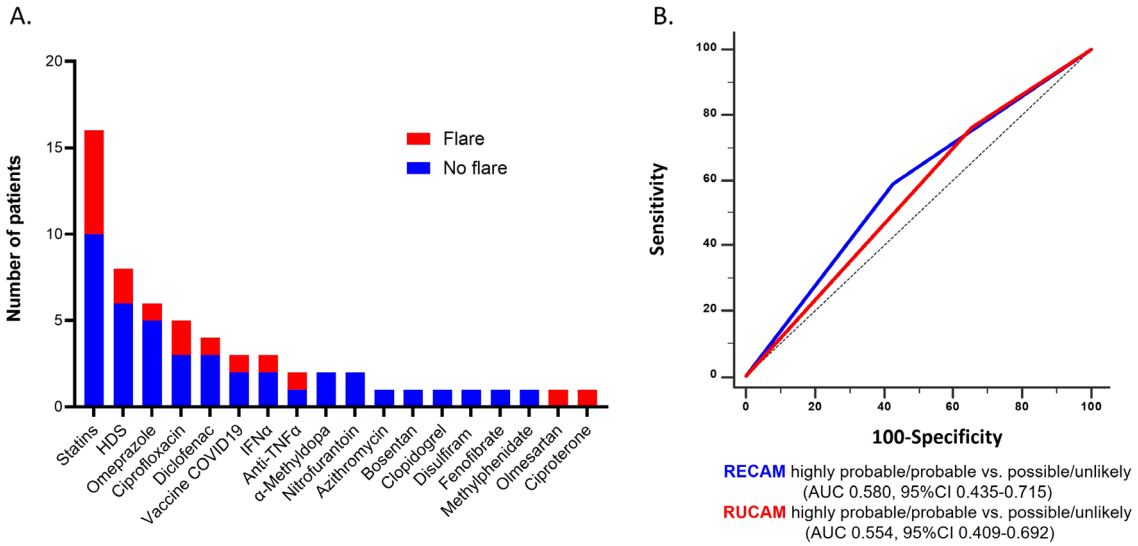

FIGURE 3 | (A) Graphical representation of the culprit drugs identified in cases of DI-ALH without flare vs. flare during follow-up. (B) ROC curves of RUCAM and RECAM for discriminating DI-ALH no-flare. No difference in the AUCs between RUCAM (AUC 0.554, 95% CI 0.409–0.692, sensitivity 76.4%, specificity 38%) and RECAM (AUC 0.580, 95% CI 0.435–0.715, sensitivity 58.8% and specificity 57.1%) was observed ($p = 0.749$). AUC, area under the curve; CI, confidence interval; HDS, herbal or dietary supplements; ROC, receiver operating curve.

considering that a significant number of patients with DI-ALH present with an acute and acute severe phenotype, the decision to withhold immunosuppression can be a "two-edge sword" for clinicians, hampering the risk of progression to ALF [7, 14, 22]. Moreover, this is further complicated by the good response to corticosteroids therapy in a proportion of patients with DILI [5]. Unfortunately, no biochemical, histological, or serological characteristics could reliably differentiate DI-ALH from i-AIH at initial diagnosis. Indeed, the presence of advanced fibrosis and cirrhosis is more frequent in i-AIH but cannot exclude the diagnosis of DI-ALH in patients with chronic drug exposure [2, 6, 23]. In fact, in our study, one patient classified as having DI-ALH had established cirrhosis, which was attributed to prolonged exposure to methylphenidate. Although methylphenidate is well recognised as a trigger of DI-ALH [1, 2], there are no prior reports of chronic liver toxicity due to this agent. Nevertheless, given the unpredictable nature of DI-ALH, its contribution could not be ruled out.

Similar to previously published studies [7], our results support that neither RUCAM nor RECAM was effective in differentiating DI-ALH, as only 34% and 46% of patients were considered as 'highly probable/probable' according to RUCAM and RECAM respectively, whereas RECAM classified 7% of DI-ALH patients as 'unlikely'. Recently, novel biomarkers such as polyreactive IgG and IgM autoantibodies (anti-ssDNA, anti-dsDNA, anti-Scl-70, and anti-U1-snRNP) have been proposed, as they appear to offer improved accuracy for the diagnosis of AIH vs. typical and autoimmune DILI cases, whereas specific HLA alleles have been associated with susceptibility to AIH (HLA-DRB1*03:01, *04:01) and certain DILI phenotypes, suggesting a potential role in differentiating i-AIH from DI-ALH or DILI. However, their efficacy in distinguishing DI-ALH remains to be investigated in larger cohorts [24–26]. The evolution of laboratory parameters during follow-up has also been proposed as a guide for treatment decisions. According to our results, patients classified as DI-ALH had lower transaminase levels at 6 and 12 months of treatment than those classified as i-AIH [1, 27]. Moreover, although the rates of CBR were the same between the groups, patients with DI-AIH achieved CBR earlier, suggesting that the sooner CBR is achieved, the more justified an attempt at immunosuppression withdrawal is [27].

However, under the current definition [1, 25], patients with DI-ALH may still experience flares, which complicates the decision to withdraw immunosuppressive treatment. Flares of DI-ALH increase over time, reaching 50% after 4 years of follow-up [7]. Whether a flare of DI-ALH signifies a perpetuation of the immune response and the evolution to a 'classic' AIH phenotype or the unmasking of a previously undiagnosed AIH is still a matter of debate [7, 8, 27, 28]. Patients presenting with flares require long-term immunosuppression [21]. In our cohort, 30% of patients with DI-ALH had a flare within a median time of 1 year, either during tapering or after complete immunosuppression withdrawal. No differences in biochemical, histological, or serological characteristics between patients with and without flares could predict the evolution of each phenotype. However, although the type and dose of immunosuppression as well as the rates of CBR did not differ between the two groups, patients without flares more frequently discontinued corticosteroids during follow-up. This observation further supports the notion that the current criteria for DI-ALH cannot completely exclude the presence of an underlying AIH, so the safest way to differentiate DI-ALH is fast tapering of immunosuppression aiming to immunosuppression withdrawal [27].

Regarding the classification tools, both RUCAM and RECAM showed low sensitivity and specificity for detecting DI-ALH without flares, highlighting a key limitation in applying these tools to patients with suspected DI-ALH. This likely reflects a conceptual mismatch, as both tools are optimised for detecting classical DILI and tend to penalise autoimmune markers. Therefore, their application in this context may systematically underestimate drug causality. Whether refinement of these tools

to account for the autoimmune phenotype could improve their accuracy in distinguishing self-limited DI-ALH from evolving AIH remains an important area for future research.

The causative agents did not differ either, as in both groups, the most frequent implicating agents were statins, followed by supplements or herbal products. These findings are in agreement with previous studies that have also highlighted statins as the most common agents associated with DI-ALH and demonstrated that no direct association between the causative agent and each phenotype can be made [5, 7]. The fact that statins are one of the most commonly used drugs worldwide may explain the difficulty in implicating them in DI-ALH and, at least in part, the misclassification of some of these cases as i-AIH.

We acknowledge that our study has several limitations. First, our results were based on a retrospective analysis; therefore, the risk of patient misclassification cannot be excluded. To minimise this risk, patients were classified after thoughtful evaluation by a panel of experts on AIH and DILI, and patients with insufficient data were excluded. Second, almost all patients received long-term immunosuppression; therefore, the prevalence of relapse in patients with DI-ALH may have been underestimated. Moreover, we included patients with at least 6 months of follow-up; therefore, the evolution of some patients in the long term is missing. Finally, although the definition of DI-ALH is based on the criteria recently established by a group of experts [1], a clear-cut distinction between DI-ALH and i-AIH remains controversial. However, to the best of our knowledge, this is the first study to evaluate the prevalence of DI-ALH in a large AIH cohort to address clinical gaps in the field.

In conclusion, a significant number of AIH patients are exposed to drugs or HDS at the time of disease diagnosis. However, a causal relationship between drugs and AIH is not routinely considered in clinical practice. Consequently, many patients who fulfil the criteria for DI-ALH are exposed to potentially unnecessary long-term immunosuppression. Therefore, a detailed history of drug exposure should be assessed in all patients with AIH at diagnosis. For patients fulfilling the criteria for DI-ALH, immunosuppression initiation should be evaluated according to each patient's characteristics, and treatment withdrawal should be attempted in all patients. In the absence of specific features and effective classification tools that can reliably differentiate DI-ALH from AIH, all patients should be maintained during long-term follow-up, considering that approximately one-third of DI-ALH cases will develop a 'classic' AIH phenotype and will require long-term immunosuppression.

Author Contributions

Pinelopi Arvaniti: conceptualization, methodology, data curation, investigation, validation, formal analysis, writing – original draft, writing – review and editing, visualization, software. **Ignasi Olivas:** data curation, investigation, writing – review and editing. **Ana Pascual-Dapena:** data curation, writing – review and editing. **Mar Riveiro-Barciela:** investigation, data curation, writing – review and editing. **Paula Esteban:** data curation, writing – review and editing. **Anna Aguilar:** data curation, writing – review and editing. **Indhira Pérez-Medrano:** data curation, writing – review and editing. **Diana Horta:** data curation, writing – review and editing. **Arancha Caballero Marcos:** data curation, writing – review and editing. **Magdalena Salcedo:** data curation, writing – review and editing. **Isabel Conde:** data curation, writing – review and editing. **Elena Gómez:** data curation, writing – review and editing. **Inmaculada Castelló:** data curation, writing – review and editing. **Jesús Santa Bárbara:** data curation, writing – review and editing. **Álvaro Díaz-González:** data curation, writing – review and editing. **Maria del Barrio:** data curation, writing – review and editing. **Sara Lorente:** data curation, writing – review and editing. **Beatriz Mateos:** data curation, writing – review and editing. **Ana Arencibia:** data curation, writing – review and editing. **Miguel Jiménez:** data curation, writing – review and editing. **Paqui Cuenca:** data curation, writing – review and editing. **Vanesa Bernal-Monterde:** data curation, writing – review and editing. **Eva-Maria Fernández:** data curation, writing – review and editing. **Sergio Rodríguez-Tajes:** data curation, writing – review and editing. **Anna Pocurull:** data curation, writing – review and editing. **Helena Hernández-Évole:** data curation, writing – review and editing. **Xavier Forns:** data curation, writing – review and editing, methodology, formal analysis, visualization. **Raul J. Andrade:** data curation, writing – review and editing, formal analysis. **Maria-Carlota Londoño:** conceptualization, methodology, software, data curation, investigation, validation, formal analysis, supervision, visualization, writing – original draft, writing – review and editing.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** apt70353-sup-0001-DataS1.docx.