

## Drug-induced autoimmune liver disease: A diagnostic dilemma of an increasingly reported disease

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### Abstract

The aetiology of autoimmune hepatitis (AIH) is uncertain but the disease can be triggered in susceptible patients by external factors such as viruses or drugs. AIH usually develops in individuals with a genetic background mainly consisting of some risk alleles of the major histocompatibility complex (HLA). Many drugs have been linked to AIH phenotypes, which sometimes persist after drug discontinuation, suggesting that they awaken latent autoimmunity. At least three clinical scenarios have been proposed that refers to drug-induced autoimmune liver disease (DIAILD): AIH with drug-induced liver injury (DILI); drug induced-AIH (DI-AIH); and immune mediated DILI (IM-DILI). In addition, there are instances showing mixed features of DI-AIH and IM-DILI, as well as DILI cases with positive autoantibodies. Histologically distinguishing DILI from AIH remains a challenge. Even more challenging is the differentiation of AIH from DI-AIH mainly relying in histological features; however, a detailed standard-

ised histologic evaluation of large cohorts of AIH and DI-AIH patients would probably render more subtle features that could be of help in the differential diagnosis between both entities. Growing information on the relationship of drugs and AIH is being available, being drugs like statins and biologic agents more frequently involved in cases of DIAILD. In addition, there is some evidence on the fact that patients diagnosed with DIAILD may have had a previous episode of hepatotoxicity. Further collaborative studies in DIAILD will strengthen the knowledge and understanding of this intriguing and complex disorder which might represent different phenotypes across the spectrum of disease

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**Key words:** Drug-induced liver injury; Autoimmune hepatitis; Drugs; Drug-induced autoimmune hepatitis; Drug-induced autoimmune liver disease

**Core tip:** Drug-induced autoimmune liver disease (DI-AILD) is a poorly defined and under-reported liver disorder, and, probably, a underestimated liver disease. A small number of drug-induced liver injury (DILI) cases exhibit features typical of autoimmune hepatitis (AIH). To differentiate between true AIH triggered by drugs (DI-AIH) and immune mediated DILI still remains a challenge. Patients diagnosed with DIAILD have frequently had a previous episode of hepatotoxicity. We consider that some basic requirements are needed to be considered before supporting a drug as a trigger of AIH and they should be taken into account by authors, reviewers and editors when cases are published and made available to the scientific community.

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## INTRODUCTION

The cause and pathogenesis of autoimmune hepatitis (AIH) is unknown<sup>[1]</sup>. AIH is characterised by the following clinical features: (1) presence of raised aminotransferases with normal or minimal elevations of alkaline phosphatase; (2) association with hypergammaglobulinemia and raised immunoglobulin G; (3) female gender preponderance; (4) high titres of a variety of autoantibodies; (5) immunogenetic background; (6) good response to immunosuppressive treatment; and (7) the presence of extrahepatic autoimmune manifestations<sup>[2,3]</sup>. In liver biopsy specimens, the presence of interface hepatitis is characteristic<sup>[3]</sup>. In 1999, an international group developed a diagnostic score system<sup>[4]</sup>, which was later on simplified in 2008<sup>[5]</sup>.

The aetiology of AIH is uncertain, but the disease can be triggered in susceptible persons by an external factor, such as viruses, drugs or herbal remedies<sup>[1,2]</sup>.

Many clinical observations suggest that drugs are potential triggers in some patients<sup>[6,7]</sup>. Several drugs have been identified to cause AIH that may persist after discontinuation, suggesting that they triggered true autoimmunity. These include oxyphenisatin, nitrofurantoin, minocycline, chlometacin and alpha-methyl dopa<sup>[3,8]</sup>. Other drugs have been infrequently reported to lead to AIH, making the association less probable. Recently, a growing number of drug-induced autoimmune liver disease (DIAILD) reports meeting the established international criteria<sup>[4,5]</sup> and showing clinical data (hypergammaglobulinemia, ANA/ASMA), typical liver biopsy findings and HLA-DR status, which allow to establish a causal relationship<sup>[6,9-11]</sup>.

For instance, Björnsson *et al*<sup>[12]</sup>, in a series of 261 patients with AIH, reported 9.2% (24 patients) of patients with drug-induced AIH. A French group<sup>[10]</sup> searched for a potential causative drug in a consecutive series of 65 patients with AIH, and identified that 12% of the cases were drug-induced, highlighting the frequency of this disorder. In this line, 5 out of 29 (17%) consecutive patients with AIH from Spain were diagnosed with drug-induced AIH<sup>[13]</sup>.

Very recently, Licata *et al*<sup>[14]</sup> reported 12 patients from a series of 136 drug-induced liver injury (DILI) subjects that were diagnosed as drug-induced AIH (8.8%). All were treated with corticosteroids and remission was achieved after six months in 10 of the cases (83%).

Although no particular drug has been definitively identified as a true aetiological trigger agent for AIH, it is interesting to note that drug-metabolizing enzymes of phase I and phase II are common targets of autoimmunity in idiopathic AIH and viral hepatitis<sup>[2]</sup>.

It is important to distinguish drugs as triggers of a self-perpetuating autoimmune liver disease from immune-mediated drug-induced liver injury (IM-DILI). Immune-mediated DILI nearly always resolves<sup>[2,12]</sup> or becomes

quiescent when drugs are withdrawn. Another possibility is that AIH was quiescent and remains undiagnosed until a drug triggered a new autoimmune process. Thus, to attempt to make a proper diagnosis of the type of immune process affecting the liver is challenging. Björnsson *et al*<sup>[12]</sup> reported 24 cases of drug-induced AIH (22 minocycline-nitrofurantoin cases, 11/11). Immunosuppressive therapy withdrawal was successful in all the 14 cases in which it was attempted. On the contrary of the AIH cases in this series 65% relapsed upon corticosteroid withdrawal. Heurgué *et al*<sup>[10]</sup>, observed one spontaneous remission, three relapses and four remissions without relapse in 8 patients out of 65 with drug-induced AIH.

In the Spanish DILI Registry, out of 742 DILI cases, 16 were diagnosed as DIAILD<sup>[9]</sup> and 25% of these cases had another autoimmune associated disease that may require persistent immunosuppressive treatment. Such cases may preclude the therapy to be discontinued and, therefore, one cannot ascertain the course of AIH upon immunosuppressive drug withdrawal. Therefore, to state that relapse after corticosteroid discontinuation might distinguish DIAILD from classical AIH is a very attractive conclusion, but far away from the complex reality of this disorder since in many cases the coexistence of other autoimmune disorders does not allow for stopping immunosuppressive therapy<sup>[15,16]</sup>. To further complicate the differentiation between AIH and DILI, we must underline the fact that there does not seem to be any specific histological features for either of the processes and the pathological features may show only subtle differences, pointing toward an immune-mediated liver disease versus hepatic toxicity<sup>[17]</sup>.

## CLASSIFICATION

There are several possible combinations of DILI and AIH (see Table 1). In 2002 Liu *et al*<sup>[2]</sup> distinguished 2 types: drugs as a potential triggers of drug-induced AIH (DI-AIH), which supposes a self-perpetuating liver disease, and immune-mediated DILI (IM-DILI), which is an acute or chronic process depending of the duration of the exposure of the liver to the hepatic insult (viruses, herbal remedies, drugs) and disappears or becomes quiescent when the drug is withdrawn<sup>[2]</sup>. In 2011, Weiler-Normann and Schramm<sup>[18]</sup> established a classification of DILI and AIH proposing possible connections with suggested diagnoses and clinical characteristics. First, AIH with DILI: The reactivation of a known AIH upon introduction of a new drug is possible, but it is very difficult to demonstrate a causal relationship, as it might be coincidental (chance by association) Often, there is advance fibrosis on histology (see Table 1). Second, DI-AIH, reveals a patient that has not been diagnosed before, or even just the predisposition to AIH that is awakened by DILI. An immune reaction in a genetically predisposed individual may lead to a chronic process, perpetuating the AIH in these patients, with a permanent need for immunosuppression. Usually, they have typical HLA-DR associated with true AIH (Table 1). Third, IM-DILI: acute

**Table 1** Classification of drug-induced autoimmune liver disease

AIH with DILI	<p>Patients with known AIH</p> <p>AIH quiescent: the drug may be the trigger of a new bout</p> <p>AIH under IS or corticosteroids treatment: Reactivation of known AIH upon introduction of a new drug (very difficult to demonstrate a causal relationship as it might be coincidental)</p> <p>Often advanced fibrosis on histology</p>
DI-AIH	<p>Patients with a low grade disease not diagnosed before or predisposition to AIH</p> <p>Drug produce an immune reaction that lead to a chronic process:</p> <p>Perpetuating the AIH</p> <p>Permanent need of IS</p> <p>Habitually typical HLA-DR associated</p>
IM-DILI (Autoimmune hypersensitivity)	<p>Fever, eosinophilia, lymphadenopathy, rash</p> <p>Indistinguishable from true AIH: Mandatory IS treatment</p> <p>Frequently spontaneous remission after drug cessation</p> <p>Usually complete response to treatment and sustained remission without relapse</p> <p>It is the most frequent drug-induced immune process in the liver attributable to drugs</p>
Mixed autoimmune type	<p>Patients with mixed clinical features of DI-AIH and IM-DILI</p> <p>Complete response to IS treatment but with chronic course after withdrawal</p> <p>Patients under IS treatment for another autoimmune disease. Withdraw IS drugs is not possible. Remission cannot be evaluated</p>
DILI with positive autoantibodies	<p>Patients with positive autoantibodies</p> <p>The probability of developing DIAILD increases in second DILI episodes independently of the causal agent</p>

AIH: Autoimmune hepatitis; DILI: Drug-induced liver injury; IS: Immunosuppressants; IM-DILI: Immunomediated DILI; DIAILD: Drug-induced autoimmune liver disease; HLA: Human leukocyte antigen.

or chronic liver injury (depending of the duration of the exposure to the drug), as has been explained by Liu and Kaplowicz<sup>[2]</sup>, that resolves or becomes quiescent with drug withdrawal. This scenario can be caused by a number of drugs, such as minocycline and nitrofurantoin<sup>[2,12]</sup>. These individuals may have spontaneous remission of acute hepatitis after drug cessation, or have a hepatocellular or mixed type of liver damage that does not improve after drug-withdrawal. Fever, eosinophilia, lymphadenopathy and rash may be present, but not always. In these situations, which are indistinguishable from true AIH, the immunosuppressive (IS) treatment is mandatory and may be life-saving. Most of these patients do not need IS forever as they usually have a complete response to treatment and a sustained remission without relapse<sup>[12,16,18,19]</sup>. This type of adverse drug reaction, which can be viewed as autoimmune hypersensitivity, is the most frequent drug-induced immune process in the liver that is attributable to drugs (see Table 1)<sup>[2,12]</sup>.

A second DILI episode (recurrent DILI) involving a different drug is a rare event, but if it happens, AIH or AIH-like DILI is frequent, and reported in up to 40% of cases in the series published from the Spanish DILI Registry<sup>[20]</sup>. Differentiating IM-DILI from DI-AIH in these cases is very difficult as the clinical presentation may be the same<sup>[20]</sup>.

Nevertheless, we think that a fourth type must be added: mixed autoimmune type. These patients have mixed clinical features that belong to DI-AIH and IM-DILI types. Thus, there are published cases of IM-DILI induced by minocycline which have a complete response to IS treatment, but experience a chronic course after drug withdrawal<sup>[15,21,22]</sup>. Therefore, the same drug can be DI-AIH or IM-DILI, depending on the clinical charac-

teristics and outcome of the episode. Another possibility is that the patient requires IS treatment for an autoimmune disease, different to AIH, in which case we cannot withdraw IS drugs. In these cases, we cannot differentiate DI-AIH or IM-DILI because the patient needs chronic IS treatment for another autoimmune disease. Therefore, one cannot ascertain the course of AIH upon IS drug withdrawal. For example, chronic uveitis has been associated with AIH<sup>[23,24]</sup>, and may require permanent IS treatment. In the Spanish DILI Registry<sup>[25]</sup>, 16 out of 742 DILI cases, were diagnosed as DIAILD<sup>[9]</sup>, 25% of these cases had another associated autoimmune disease, which may require persistent IS treatment. In a French series of eight patients<sup>[10]</sup>, 25% of them had another AI associated disease.

Finally, there are patients that present DILI with positive autoantibodies. However, its significance is unknown and requires further studies. In 2002, Ohmoto and Yamamoto studied 64 patients admitted to their hospital with DILI and identified 6 with positive ANA<sup>[26]</sup>. They found a higher prevalence of associated autoimmune diseases in the ANA positive group such as AIH, rheumatoid arthritis, Hashimoto's disease. The authors suggested that patients with DILI and ANA might also have autoimmune disease and should be followed over the long-term, even if liver function has recovered. On the other hand, Hinrichsen *et al.*<sup>[27]</sup> reported a case of phenprocoumon-induced hepatitis with positive autoantibodies. After the drug was stopped, no clinical or laboratory features of autoimmune liver disease were present.

Recently, the Spanish-Latin American DILI Network has published a series of 73 DILI cases, in which 29% presented positive autoantibodies, mainly ANA. Six cases were DIAILD (AIH DILI) (8%) and 5 cases (7%) had

experienced a second DILI episode<sup>[28]</sup>.

Therefore, this analysis further support that the probability of presenting positive antibodies increases in second DILI episodes, as previously shown by Andrade *et al*<sup>[29]</sup>.

## HISTOLOGY

Liver histology shows apoptosis, necrosis and inflammatory infiltrates including mononuclear cells, neutrophils, eosinophils and lymphocytes, or cholestasis and paucity of bile ducts with moderate portal inflammation. Granulomas may also be seen<sup>[2]</sup>. Distinguishing DILI from AIH is challenging histologically. Recently, Suzuki *et al*<sup>[17]</sup> showed that while a histologic overlap exists for these pathologies, sufficient differences exist for pathologists and they can use the pattern of injury proposed by Suzuki *et al*<sup>[17]</sup> to suggest a correct diagnosis. Interface hepatitis, focal necrosis and portal inflammation were present in all of the evaluated cases but were more severe in AIH than in hepatocellular DILI. Portal and intra-acinar plasma cells, rosette formation, and emperipolesis were features that favoured AIH. All Ishak inflammation scores were more severe in AIH than in cholestatic DILI. They did not identify any histologic features differentiating AIH from DIAILD (DI-AIH) in a small subgroup analysis (7 cases), but it might still be possible that detailed standardised histologic evaluation using a larger cohort of DIAILD (DI-AIH) *vs* AIH can identify histologic features that can be helpful in the differential diagnosis. Björnsson *et al*<sup>[12]</sup>, in a recent work, revealed that similar histological grades and stages were present in patients with IM-DILI (DI-AIH) *vs* AIH. However, none of the IM-DILI (DI-AIH) patients had cirrhosis at baseline and it was present in 20% of the AIH patients. Czaja<sup>[16]</sup>, based on the referred work, confirmed that cirrhosis is a rare histologic feature in nitrofurantoin AIH cases at presentation, which may help to distinguish it from classical AIH (0 *vs* 13%). In a recent review of the histological patterns found in cases of DILI<sup>[30]</sup>, it was pointed out that, contrary to minocycline, significant fibrosis and cirrhosis occurs with nitrofurantoin. The French group<sup>[10,31]</sup> biopsied all of their cases (Minocycline *n* = 3; nitrofurantoin *n* = 2; atorvastatin *n* = 1; fenofibrate *n* = 1; isotretinoin *n* = 1), showing a fibrosis score F3-F4 in 57% *vs* 48% in the DIAILD (AIH-DILI) and AIH groups, respectively. Necroinflammatory activity A3, with Metavir, was revealed in 75% *vs* 65%. They concluded that the 2 groups showed similar histological lesions of fibrosis/cirrhosis. Recently, Licata *et al*<sup>[14]</sup> studied a series of 12 patients (4 nimesulide, 1 ketoprofen, 3 amoxicillin-calvulanate, 1 ceftriaxone, 1 epigallocatechin gallate and 1 hypericum perforatum-herbal drugs-, and dimethoate-toxic agent). All DIAILD patients were treated with corticosteroids and none developed cirrhosis. Appleyard *et al*<sup>[32]</sup> published a series of 3 cases, one of which had pre-cirrhosis/cirrhosis at diagnosis. The Spanish Registry of Hepatotoxicity<sup>[9]</sup> presented a case report of DIAILD that showed cirrhosis in the liver biopsy at presentation. Therefore, the absence of histological cirrhosis at presentation would not help to

discern between these two entities.

Ju *et al*<sup>[33]</sup> have studied the histological features of DILI patients in Korea, with special focus on relevancy of AIH. The study showed that characteristic histologic features of AIH, as interface hepatitis and lymphoplasmocytic infiltrates, were present in up to one third of DILI patients.

## FREQUENCY

Recently Czaja<sup>[16]</sup> stated that the best estimate of the frequency of drug-induced autoimmune-like hepatitis among patients with classical features of AIH is 9%<sup>[12]</sup>. There are other reports that show higher figures<sup>[15]</sup>. Heurgué *et al*<sup>[10]</sup>, in France, identified 8 cases (12%) with drug-induced AIH in a consecutive series of 65 patients with AIH, fulfilling all requirements recommended in the review to confirm the diagnosis (Table 2). In Gipuzkoa, Spain, from 1994 to 2009, 29 cases of AIH were diagnosed, 5 of which were considered AIH-DILI, which resulted in a 17% frequency<sup>[13]</sup>. We believe that these differences in frequencies may be explained by the fact that AIH-DILI is often misdiagnosed.

If we study patients diagnosed with DILI, Licata *et al*<sup>[14]</sup> reported 8.8% of the patients presenting features of DIAILD (DI-AIH). In the Spanish DILI Registry<sup>[9]</sup>, out of 742 recruited cases, 16 presented DIAILD criteria (2.15%).

### Why is there a growing number of case reports?

Indeed, the diagnosis of AIH is often made in the setting of a patient being treated with multiple drugs. If the diagnostic scale points out probable AIH, the possible role of the drug is generally underscored, and immunosuppressive treatment is started. On the other hand, if the AIH scale is not conclusive and/or histology findings are more consistent with DILI, the case is assumed to be a DILI case, particularly if the clinical symptoms resolve after discontinuation of the suspected drug (DIAILD may be a self-limiting process), and the possibility of unmasking AIH by the action of a drug is disregarded. To further complicate the differentiation between AIH and DILI we must underline the fact that there is no specific histological features of either process and the pathological features may show only subtle differences pointing to the immune-mediated liver disease versus hepatic toxicity<sup>[17]</sup>. These considerations lead us to suggest that DIAILD might be underreported nowadays.

When a patient is admitted to hospital because of acute hepatitis and the drug that is thought to be responsible is identified, treatment is stopped.

If transaminases decreased more than 50% in 1 week to 1 month, and the DILI case fulfils other Council for International Organizations of medical Science (CIOMS) criteria such as a favourable temporal sequence, alternative pharmacological and clinical conditions have been ruled out, dechallenge with the drug is followed by improvement, and rechallenge if present is positive, then the DILI case is probably related to the drug<sup>[34,35]</sup>. Sponta-

neous recovery supports this possibility and, generally, if autoantibodies have been solicited to the laboratory and are positive, we do not consider the possibility of a drug as a trigger of IM-DILI.

If aminotransferases remain permanently raised, suffer an increase during follow-up, and autoantibodies are positive, AIH is assumed; if the AIH-scale reveals a probable AIH, treatment with IS is begun as soon as possible. There is complete exclusion of the trigger paper of a drug treatment if it is present prior to acute hepatitis, or if the drug is retired but without giving its importance to it; if true, AIH may resolve spontaneously.

New drugs: the growing use of drugs such as statins and biologic agents, which have been related to DILI with autoimmune features, which has prompted an increase in the diagnosis of DIAILD<sup>[36-42]</sup>.

The diagnosis DIAILD represents a challenge to the clinician as there are neither histological, nor clinical features that are pathognomonic of true AIH, and HLA haplotypes do not convincingly distinguish between either entity. Indeed, as previously commented many cases of drug-induced AIH tend to be misdiagnosed as classical AIH cases. The CIOMS scale is unable to distinguish between AIH and DIAILD, as the scale fails to accommodate all relevant information for diagnosing DIAILD. Causality may also be challenged by the lack of spontaneous improvement after drug withdrawal in this form of DILI.

## PREDICTION OF AUTOIMMUNE HEPATITIS-RISK FACTORS

### Susceptibility

**Autoantibodies:** Many autoimmune diseases are chronic conditions that progress over the years, and are characterised by the presence of autoantibodies that may precede the overt disease by months or years<sup>[43]</sup>. In AIH, the hallmark is the presence of circulating autoantibodies. If ANAs are detected in female patients with DILI, the co-existence of an autoimmune disease is possible<sup>[26]</sup>.

**HLA genes and haplotypes:** Susceptibility to AIH, via a genetic predisposition, has been clearly associated with class II human leukocyte antigen (*HLA*) genes, more specifically to the DRB1 locus<sup>[44]</sup>. This is the major associated gene locus. Predisposition to AIH type I is associated with HLA-DRB1\*0301, DRB3\*0101, and DRB1\*0401 alleles in European and North-American Caucasoid, encoding the HLA-DR3, DR52 and DR4 molecules, respectively. Czaja *et al.*<sup>[45]</sup> determined in 1993 the following class II HLA associations with AIH: 44% DR3, 32% DR4, 9% DR3-DR4, and 15% other antigens. The study of different geographical areas and ethnic groups revealed different results. In Japan and Argentinian Caucasoid adults, susceptibility was associated with HLA-DRB1\*1-0405 (DR4): Mexican adults presented DRB1\*0404 (DR4), and Caucasoid children and adults from Argentina presented DRB1\*1301 (DR13)<sup>[45-49]</sup>. In Brazil, the haplotype DRB1\*1301 is the most frequently

related to type 1-AIH<sup>[44]</sup>. A secondary association with HLA-DRB1\*0301 has been detected in this country<sup>[50]</sup>. Another haplotype, DRB1\*07, seems to produce susceptibility in German and Brazilian populations<sup>[51,52]</sup>. Type 2 AIH is associated with the haplotypes HLA-DRB1\*0301 and HLA-DRB1\*07<sup>[50]</sup>. Recently, Oliveira *et al.*<sup>[50]</sup> searched for additional susceptibility factors in the extended MHC region. They have studied genes located in the MHC class III region, in addition to class I HLA-B and MICA genes, to verify if the specific haplotypes DRB1\*1301 or DRB1\*0301 could be involved in the susceptibility of paediatric patients in Brazil<sup>[53]</sup>. The ancestral haplotype comprising *TNFA*-308A, *TNFA*-238G, *LTA*+252G, *LTA*+80C, *NFKBIL1*-63A, *BAT1*-348C, *BAT1*-22C, *HLA-B*\*08 and *MICA*\*08 was more common in DRB1\*03 positive patients than in controls (40% *vs* 14%), showing a seven-fold increased risk of disease. Finally, a variety of class III haplotypes was also present in HLA-DRB1\*13 patients, without a predominant pattern. The most common of the 98 haplotypes present in patients were completely absent in controls. The extended haplotype analysis in this sample of AIH-1 patients highlighted not only the genetic diversity present in the Brazilian population, and was also in accordance with the previously documented microdiversity within the MHC region. The DRB1\*1501 allele may protect from disease<sup>[46]</sup>.

### Triggers

Triggers may induce AIH. AIH may be induced by drugs<sup>[12]</sup>, herbal remedies<sup>[11]</sup>, different viruses and bacteria<sup>[54-58]</sup> and vaccines<sup>[59,60]</sup>.

Exposure to all of these potential triggers may produce immune responses that especially target the liver, mainly in predisposed individuals, as we have seen previously; therefore, chronic hepatitis with autoimmune features might develop. If not recognised promptly and the responsible agent is not withdrawn, such responses can evolve to chronic hepatitis (resembling viral hepatitis) - alpha-metil dopa, halothane, hydralazine, minocycline, nitrofurantoin, and oxyphenisatin - or to a chronic non-suppurative cholangitis (resembling PBC) - chlorpromazine<sup>[1]</sup>.

Identification of these risk factors might help us to think about this disease and halt treatment with the offending trigger as soon as possible. Withdrawal of the offending agent may lead to a rapid resolution of the process.

**Genetic polymorphisms:** Several genetic polymorphisms of drug metabolising enzymes, particularly CYP, have been identified, which may produce reactive metabolites<sup>[2]</sup>. Differences in the metabolism of drugs genetically conditions may produce protein adducts and susceptibility to DI-AIH. The occurrence of more than one case within a family supports the theory that genetic factors are involved<sup>[61]</sup>. It has been shown that a familiar sensitivity to the toxic effect of the metabolites exists, which may produce an inherited defect in the defence of

**Table 2** Elements to be reported when a case of drug-induced autoimmune liver disease is suspected

Previously obtained ANA
Evolution:
During the treatment with the suspicious drug
After drug withdrawal
Check for the presence of HLA-DR:
HLA-DRB1*0301,0401,07,1301
Drug type
Time to onset from the beginning of the treatment
AIH diagnosed:
During the course of treatment
After withdrawal of the drug
AIH scales for diagnosis
International autoimmune hepatitis group report (4)
Simplified score (5)
Previous DILI episodes
Response to corticosteroids
Autoimmune titres evolution
IgG values evolution

AIH: Autoimmune hepatitis; DILI: Drug-induced liver injury.

the liver from the injury produced by these toxic metabolites<sup>[2]</sup>. Anti-convulsants and sulphonamides have shown a familiar inheritance of *in vitro* lethal effects against the lymphocytes by their metabolites<sup>[62,63]</sup>.

### Sex

In AIH, there is a female sex predominance. Women are affected more frequently than men (sex ratio 3.6:1) and the disease is seen in all ethnic groups and across all age intervals<sup>[56]</sup>. Björnsson *et al.*<sup>[12]</sup> published 78% (184/237) of females with AIH *vs* 92% in the DI-AIH (20/24); in the nitrofurantoin group the findings were 11/11, with numbers of 10/11 in the minocycline group. In the Spanish DILI Registry, sixteen cases out of the 742 cases (2.15%) of idiosyncratic DILI were identified<sup>[9]</sup>. There were 10/16 women. Heurgué *et al.*<sup>[10]</sup> reported 8 patients with DI-AIH out of 65 AIH cases diagnosed consecutively. The female/male sex ratio was 87% *vs* 82%, revealing no statistically significant differences. Sugimoto *et al.*<sup>[11]</sup> recently published a series of 7 patients with AIH that developed after a first DILI episode. Six out of the seven affected patients were women. In other smaller series, a female preponderance seems to be the general rule<sup>[32]</sup>. Czaja *et al.*<sup>[16]</sup> reported that not only does DIAILD (DI-like AIH) occur almost exclusively in women, but that the drug injuries in the liver are more severe than in men<sup>[2,12,64,65]</sup>. Indeed, female sex has been found to be a risk factor for acute liver failure development after a DILI episode<sup>[25]</sup>.

### DILI

Multiple episodes of DILI in the same patient with drugs of similar structure or function as well as unrelated drugs may induce immune-related hepatotoxicity<sup>[20]</sup>. Between 1994 and 2009, Lucena *et al.*<sup>[20]</sup> identified 9 patients out of 742 in the Spanish DILI Registry (1.21%), with evidence of two distinct DILI episodes produced by different drugs. In each individual, the type of injury was the same

in the two episodes, regardless of the causative drug. Second episodes were associated with features of AIH up to more than 40% (4/9) of cases, making it unclear whether this is drug-induced unmasking of true DI-AIH or IM-DILI (DILI with autoimmune features).

### Age

Elderly individuals have an increased risk of drug toxicity<sup>[16]</sup>. The risk of DILI increases with age for certain drugs, such as those that are implicated in autoimmune-like hepatitis (nitrofurantoin, halothane, and isoniazid).

### Association with other autoimmune diseases or induction by biologic agents

**Biologic agents:** Biologic agents are increasingly being used for rheumatological and systemic autoimmune diseases. The BIOGEAS project<sup>[39,40]</sup>, created by the Spanish Society of Internal medicine, has retrieved more than 800 cases of AI diseases secondary to biological therapies. In this study, 19 cases of AIH have been reported. Statins<sup>[36,37]</sup> have been reported to induce AI diseases, typically in patients with other AI diseases.

**Spontaneously:** AI diseases frequently appeared to be associated between them<sup>[36,37]</sup>. Multiple examples are published in the literature<sup>[66]</sup>.

### Drugs

Nowadays, more than 900 drugs, toxins and herbal remedies have been reported to cause liver injury. Recently, it has been reported that at least 24 drugs, probably more, have been associated with AI chronic hepatitis mimicking AIH<sup>[67]</sup>, but more and more new agents are being implicated<sup>[67-83]</sup>. With the appearance of new statins, biologic agents, and antibiotics, it will be quite normal to see more new agents being reported as being responsible for new drug-induced AIH cases (Table 3).

### Elements to be reported when a case of DIAILD is suspected

Some basic requirements are needed to consider a drug as a trigger of AIH. These basic requirements must be debated and consensuated prior to the publication of a suspected new case. The elements that we think that must be included in a suspected DIAILD case before publication are outlined in Table 2.

## CONCLUSION

DIAILD is still a poorly defined and under-reported liver disorder and is also a probably underestimated liver disorder. A small number of DILI cases exhibit features typical of AIH. To differentiate between true AIH triggered by drugs (DI-AIH) and IM-DILI still remains a challenge. Patients diagnosed with DIAILD have frequently had a previous episode of hepatotoxicity. The CIOMS scale has a limited value to ascertain causality in DIAILD. Hopefully, the collaborative efforts in DILI research will

**Table 3** Drugs and drug-induced autoimmune liver disease

Well established drugs:
Minocycline
Nitrofurantoin
Oxyphenisatin, alpha-methyl-dopa, clometacin.
Emerging drugs:
Statins
Biologics agents:
Infliximab
Others: adalimumab, etanercept, efalizumab, ipilimumab
Other drugs:
Less compelling association (infrequent reports): atomoxetine, diclofenac, fenofibrate, pemoline, phenprocoumon, dihydralazine, tielinic acid, benzarone

enhance our knowledge of this intriguing hepatic disease. We consider that some basic requirements are needed to be considered before supporting a drug as a trigger of AIH and they should be taken into account by authors, reviewers and editors when cases are published and made available to the scientific community.

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