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ORIGINAL ARTICLE

Discontinuation of immunosuppression in patients with immune-mediated drug-induced liver injury or idiopathic autoimmune hepatitis: A case–control study

Jeremy Hassoun,* Nicolas Goossens,* Sophie Restellini,* Lucas Ramer,* Marie Ongaro,* Emiliano Giostra,* Antoine Hadengue,* Laura Rubbia-Brandt† and Laurent Spahr*

Departments of *Gastroenterology and Hepatology and †Clinical Pathology, University Hospitals of Geneva and Faculty of Medicine, Geneva, Switzerland

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Correspondence
Prof Laurent Spahr, Department of Gastroenterology and Hepatology, University Hospitals of Geneva (HUG), Floor P, 4, Rue Gabrielle Perret-Gentil CH-1205, Geneva, Switzerland.
Email: laurent.spahr@hcuge.ch

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Abstract

Background and Aim: Drug-induced liver injury (DILI) may present with autoimmune features and require immunosuppressive therapy (IST) to reach biochemical response. Discontinuation of IST without hepatitis relapse may be more frequent in these patients as compared to patients with classical autoimmune hepatitis (AIH). We aimed to determine baseline characteristics and outcome of patients with immune-mediated drug induced liver injury (IMDILI) with particular emphasis on IST during follow-up.
Methods: We performed a single-center retrospective study of consecutive patients presenting at a tertiary care center between January 2005 and December 2019 either with IMDILI or with classical AIH, for whom full baseline characteristics and a close follow-up were available over a 12-month period.
Results: Overall, 31 patients (IMDILI $n = 16$, mean age 59 [34–74] years; AIH $n = 15$, mean age 47 [15–61] years) were included, showing similar biochemical, serological, and histological characteristics. Incriminating drugs in IMDILI patients were mostly represented by nonsteroidal antiinflammatory drugs and sartans. Initial corticosteroids combined with IST led to biochemical response in all patients. Compared to idiopathic AIH, more patients with IMDILI were weaned off corticosteroids at the end of follow-up (11/16 [68.7%] *vs* 4/15 [26.6%], $P < 0.02$). At 1 year of follow-up, more patients in the IMDILI group compared to the classical AIH group were off any type of IST (13/16 [81%] *vs* 15/15 [100%], $P = 0.08$).
Conclusions: Although presenting with similar baseline biochemical and histological characteristics as idiopathic AIH, patients with IMDILI may not require long-term IST.

Introduction

Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease of ill-defined etiology, characterized by circulating autoantibodies, typical histological alterations, and response to immunosuppressive therapy (IST).[1] Arriving at a diagnosis of AIH may be challenging, as it requires the exclusion of other causes of liver injury, and the presence of autoantibodies is not specific for the diagnosis.[2] Therefore, a diagnosis of AIH is usually made using a combination of biochemical, immunological, and histological characteristics with the exclusion of alternative diagnoses including viral hepatitis.[3] The mechanisms underlying this autoimmune liver inflammation are still elusive. However, an antigen-driven, autoimmune, T-cell mediated response targeting an unknown hepatic molecular target

in genetically susceptible individuals is a plausible scenario.[4] The environmental antigens that may trigger such an immune reaction may include viruses and drugs. Drug-induced liver injury (DILI) is a major cause of liver injury worldwide, ranging from asymptomatic elevation of liver function to acute liver injury.[5] Mechanisms of drug hepatotoxicity may be dose-related, as in acetaminophen liver toxicity, or unpredictable and leading to a so-called immunoallergic reaction without definite risk factors.[6] Pathogenic mechanisms associated with idiosyncratic liver injury include a disproportionate immune-mediated inflammatory response to some drug-related products or metabolites. Such an acute immune reaction may perpetuate liver inflammation and damage, therefore mimicking autoimmune liver injury.[6-8] This particular situation named immune-mediated DILI (IMDILI) combines increased serum transaminases, elevated gammaglobulins, detectable autoantibodies, and histological alterations suggestive of idiopathic AIH.[9] Therefore, it may be challenging to distinguish between AIH and IMDILI,[10] although both situations initially require IST and close monitoring of biochemical test results.[1,11,12] It has been reported that withdrawal of IST is more frequently achieved during follow-up in IMDILI compared to AIH,[10] but data are scarce and clinical outcome is inconstant, and thus the question remains open.

Therefore, we aimed to determine the clinical outcome of patients with acute liver injury related to idiopathic AIH or IMDILI, with particular emphasis on IST during follow-up.

Methods

This was a retrospective analysis of patients with a diagnosis of idiopathic classical AIH or IMDILI whose data were collected from the medical records of the Liver Unit of the University Hospital of Geneva, a tertiary care center in southwestern Switzerland. The study was performed in accordance with the guidelines of the 1975 Declaration of Helsinki and was approved by our local institutional review board (CCER 2015-15-265, BASEC 2015-00075). We reviewed all cases between January 2005 and December 2019, and selected patients (IMDILI) and controls (AIH) based on the following inclusion criteria: (i) acute liver injury with a liver biopsy available at diagnosis; (ii) full baseline biochemical parameters prior to initiation of IST; (iii) detailed history of drug administration prior to hospital admission; and (iv) close monitoring during a 12-month follow-up (clinical and biochemical data). Patients were excluded (i) if there was present a coexistent liver disease of other etiology (alcohol, other), (ii) if there was chronic decompensated liver disease, (iii) if the follow-up could not be completed, or (iv) if liver transplantation occurred during the follow-up period.

We extracted the following variables from the patients records: usual demographic characteristics; serological markers of viral hepatitis; history of associated autoimmune disorders; liver function tests; serum levels of anti-smooth muscle antibody (SMA), anti-nuclear antibody (ANA), and immunoglobulin G (IgG); type and dosage of IST; and identification of a drug with recent (i.e. within weeks) exposure and suspected as a trigger for IMDILI. Particular attention was paid to drugs[12-14] or complementary alternative medicines (such as natural products)[7,15] that have been reported to cause DILI with AI features.[16] Results of human leukocyte antigen (HLA) typing and lymphocyte transform test were not available. In addition, liver biopsy was analyzed for typical features of AIH. These data at baseline were used for the diagnosis of AIH.[3]

Liver biopsy result was examined in detail by a senior pathologist who is an expert expert in liver diseases (LRB) who was unaware of the patients' clinical characteristics, drug history, and clinical outcome. We used a semi-quantitative evaluation of histological features that are typically observed in AIH, derived from previous studies.[3,12] Thus, the severity of portal tract inflammation and lobular hepatitis were scored as 0 (=absent), 1 (=mild), or 2 (=severe), while lymphoplasmocytic infiltration, interface hepatitis, confluent necrosis, and rosette formation were assessed as present (=1) or absent (=0). Liver fibrosis was graded as none (=0), portal or periportal (=1), and bridging or cirrhosis (=2).

If a recent exposure (i.e. within weeks) to a drug/natural product suspected of being a trigger for the acute hepatitis was documented in the medical records, then the patient was included in the IMDILI group. The Roussel-UCLAF Causality assessment scale was applied in cases of suspected DILI.[17]

Thus, the diagnosis of IMDILI was accepted when the following conditions were fufilled: (i) a recent exposure to a drug suspected of being a trigger for the acute hepatitis; (ii) a causality score considering the temporal relationship between the drug and the liver injury at least as probable; and (iii) a liver biopsy showing typical histological features of AIH.

Initial clinical management included a liver biopsy performed early after hospital admission (within days) and early initiation of IST using frontline therapy (corticosteroid treatment including prednisolone and budesonide), which was then combined with immunosuppressive drugs including azathioprine or mycophenolate mofetil,[18] as recommended.[19] Examination at each visit by a senior hepatologist (A.H., E.G., L.S., N.G.) included liver transaminases, IgG, and total bilirubin levels, which were extracted from the medical records, as well as the type and dosage of IST. We aimed at gradually decreasing IST to the lowest possible dose to maintain biological response. Weaning off prednisolone was a priority given the undesirable side-effects of steroids. Thus, under close monitoring of transaminases, steroids were tapered down if possible, while azathioprine or mycophenolate was maintained at the lowest dosage. If biological remission was maintained over time, steroids were then stopped and other immunosuppressants were retained for maintenance therapy, as recommended by international guidelines.[19] Close monitoring included prevention of cytopenias and control of liver enzymes.

An increase of more than twice the upper limit of normal alanine aminotransferase (ALT) level was considered as a relapse or flare of the hepatitis[7] and an indication to increase IST.

Statistical analyses. Continuous variables are presented as median and range. Categorical parameters are expressed as percent with mean value and SD. Pearson's test and Fisher's exact test were used to compare qualitative and categorical variables. Comparison of the two groups over time in terms of exposure to IST and steroids was done using the log-rank test. We used the two-way repeated-measures ANOVA to assess changes in ALT, IgG, and bilirubin levels between baseline

and follow-up visits in the two groups. All statistical analyses were performed using SPSS version 20.0 (IBM SPSS Statistics). All tests were two-tailed and considered significant at $P < 0.05$ level.

Results

Clinical and biological characteristics. Ninety-seven patients were identified in our database with a diagnosis of acute liver injury due to AIH. For a number of reasons, only 31 patients fulfilled the inclusion criteria and had available data for analysis (see Fig. 1). Thus, there were 15 patients in the classical AIH group and 16 patients in the IMDILI group. Table 1 describes patient characteristics at baseline; all of them had jaundice and elevated liver transaminases with a relatively preserved coagulation function. Except for a slightly younger age in patients with AIH, both female gender preponderance and associated autoimmune features were not statistically different between groups. Nevertheless, there was a tendency toward more autoimmune diseases in patients with AIH (Hashimoto thyroiditis, leukocytoblastic vasculitis, Sjögren syndrome, myasthenia gravis) compared to patients in the IMDILI group (systemic lupus erythematosus, Sjögren syndrome), as previously reported.[20] Baseline biological values in both groups showed high transaminases levels (above 3 ULN), moderate elevation in alkaline phosphatase (ALP) and INR (international normalized ratio), marked increase in serum bilirubin, and elevated IgG levels. Similar positivity rates for ANA and SMA were observed in patients in the IMDILI (81% and 62%, respectively) and AIH (67% and 87%, respectively) groups. A score compatible with the diagnosis of AIH[3] was obtained in four patients (two in each group) due to the absence of elevated autoantibody titers, normal or near-normal IgG serum level, or mild intensity of histological lesions. Long-term follow-up period was not statistically different between groups.

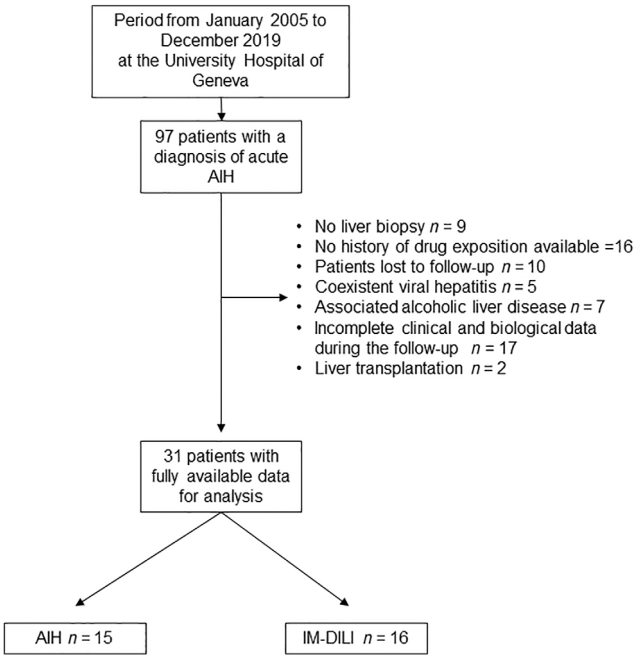

Figure 1 Flowchart of patients selection.

Table 1 Baseline characteristics of patients

Variable	IMDILI	AIH	*P*-value
n	16	15	0.81
Age (years, range)	59 (34–74)	47 (15–61)	0.01
Female gender (%)	80	75	0.19
Associated autoimmune disorders (*n*, %)	2 (12.5)	6 (40)	0.08
AST (IU/L, *n* < 48)	1073 (409–1662)	909 (67–2077)	0.49
ALT (IU/L, *n* < 55)	1071 (472–1799)	915 (117–2231)	0.43
ALP (IU/L, *n* < 115)	158 (68–290)	153 (71–345)	0.86
INR (*n* < 1.2)	1.26 (1–1.9)	1.34 (1–3)	0.63
Bilirubin (μmol/L, *n* < 21)	203 (14–541)	130 (7–340)	0.13
IgG (g/L, *n* < 15)	24.7 (14.9–41.6)	30.7 (13.8–57.5)	0.15
ANA positive (%)	81	67	0.65
SMA positive (%)	62	87	0.50
Both ANA and SMA positive (%)	31	60	0.11
Probable/definite AIH (*n*, %)	14 (87.5)	13 (87)	0.94
Total follow-up period in months (median and range)	49.4 (12–110)	79.1 (12–187)	0.85

Probable or definite AIH is based on simplified criteria for AIH (3).
AIH, autoimmune hepatitis; ALT, alanine aminotransferase; ALP, alkaline phosphatase; ANA, antinuclear antibody; AST, aspartate aminotransferase; IgG, immunoglobulin G; SMA, smooth muscle antibody.

Table 2 Histological lesions at baseline liver biopsy

Histological feature	IMDILI	AIH	*P*-value
Portal inflammation (*n*, %)			
Absent or mild	12 (75)	13 (87)	0.63
Severe	4 (25)	2 (13)	0.69
Lobular hepatitis (*n*, %)			
Absent or mild	11 (69)	14 (94)	0.18
Severe	5 (31)	1 (6)	0.17
Fibrosis stage (*n*, %)			
Absent or periportal	15 (94)	14 (93)	0.9
Bridging or cirrhosis	1 (6)	1 (7)	0.9
Lymphoplasmocytic infiltrate (*n*, %)			
Absent	1 (6)	4 (27)	0.36
Present	15 (94)	11 (73)	0.33
Interface hepatitis (*n*, %)			
Absent	7 (44)	6 (40)	0.98
Present	9 (56)	9 (60)	0.99
Confluent necrosis (*n*, %)			
Absent	4 (25)	6 (40)	0.48
Present	12 (75)	9 (60)	0.52
Rosette formation (*n*, %)			
Absent	15 (94)	14 (93)	0.98
Present	1 (6)	1 (7)	0.98

AIH, autoimmune hepatitis; IMDILI, immune-mediated drug induced liver injury.

Table 3 Drugs suspected as a trigger in patients with IMDILI

Suspected drug	Class of medication	No. of patients
Mefenamic acid	NSAID	1
Ibuprofen		5
Olmesartan	Sartans	1
Candesartan		1
Valsartan		1
Fosfomycin	Antibiotics	1
Nitrofurantoin		1
Trazodone	Antidepressants	2
Echinacea angustifolia	Complementary alternative medicine	1
Ibandronate	Biphosphonate	1
Enalapril maleate	Antihypertensive	1

IMDILI, immune-mediated drug induced liver injury; NSAID, non-steroidal antiinflammatory drug.

Histology. Liver biopsy findings that are typical of AIH, such as interface hepatitis, portal inflammation, rosette formation, and lymphoplasmocytic infiltration, were present in both groups, with a tendency toward more severe plasma cell infiltration in the AIH compared to the IMDILI group. Lesions of lobular hepatitis and areas of necrosis were found in all patients. Except for one patient in each group with bridging fibrosis, liver fibrosis was absent or limited to the portal or periportal area (see Table 2). Thus, both AIH and IMDILI showed similar histological features on liver biopsy, consistent with previous observations.[12]

Suspected causative drugs. Drugs that have been identified as a possible trigger for acute liver injury in the IMDILI group included nonsteroidal anti-inflammatory drugs (NSAIDs), antihypertensive agents, antibiotics, antidepressants, biphosphonate, and a complementary alternative medicine agent, most of them being reported in a recent publication.[16] Details of the drugs and the number of affected patients are given in Table 3. According to the CIOMS-RUCAM scale, which considers the temporal association between exposure to a suspected drug and the occurence of liver injury,[17] causality score for DILI in IMDILI patients was 7.3,[6–10] indicating a "probable" to "very likely" relationship.

Table 4 Type of immunosuppressive therapy during follow-up

Type of IST	IMDILI ($n = 16$)	AIH ($n = 15$)
Frontline therapy (n=)		
Prednisolone 0.5–1 mg/kg/day	13	13
Budesonide 9 mg/day	3	2
Azathioprine 50 mg/day up to 1–2 mg/kg/day	8	10
Mycophenolate mofetil 1000 to 2000 mg/day	7	5
Maintenance therapy (n=)		
Prednisolone 0.5 mg/kg/day	0	0
Budesonide 3 to 6 mg/day	1	0
Azathioprine 0.5–2 mg/kg/day	9	11
Mycophenolate mofetil 1000–2000 mg/day	6	4

AIH, autoimmune hepatitis; IMDILI, immune-mediated drug induced liver injury; IST, immunosuppressive therapy.

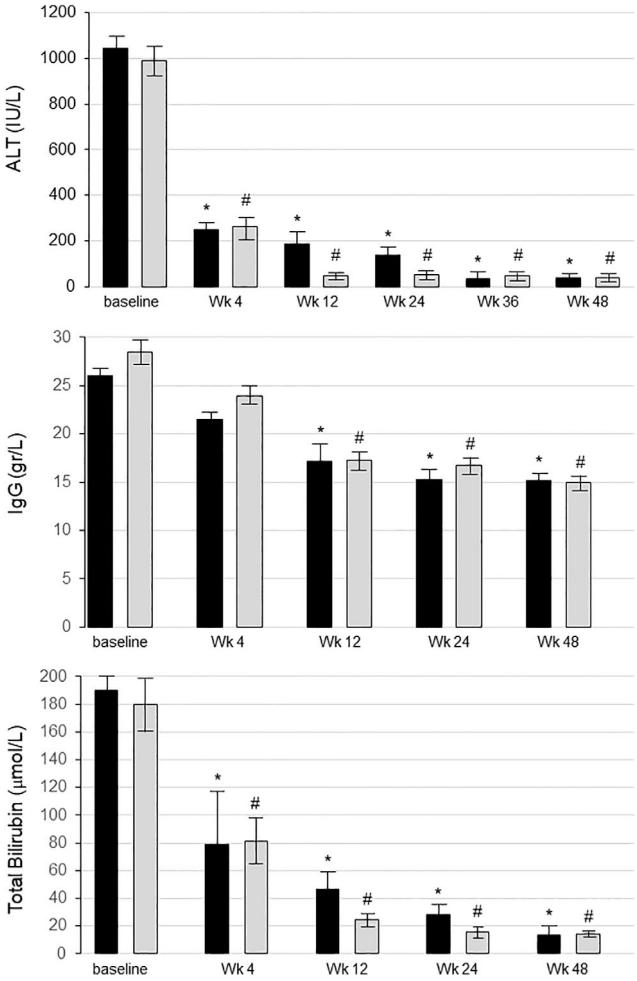

Figure 2 Evolution of alanine aminotransferase, immunoglobulin G, and bilirubin serum levels during the follow-up period in patients with immune-mediated drug induced liver injury (IMDILI) (in black) and in patients with autoimmune hepatitis (AIH) (in gray). * and # indicate $P < 0.05$ in comparison with baseline values in IMDILI and AIH groups, respectively.

Biological evolution. All patients received initial frontline therapy to which a steroid-sparing agent was added in the days following hospital admission. Table 4 summarizes the type of IST administered early in the course of the disease as well as during the maintenance phase. No re-exposure to the incriminating drug was detected in the IMDILI group during follow-up. The lowest possible dose of IST was administered to maintain biochemical remission and to ensure the best tolerance to treatment. As shown in Figure 2, we observed a parallel evolution of ALT, IgG, and total bilirubin serum levels over time without statistical differences between the groups. A relapse during IST

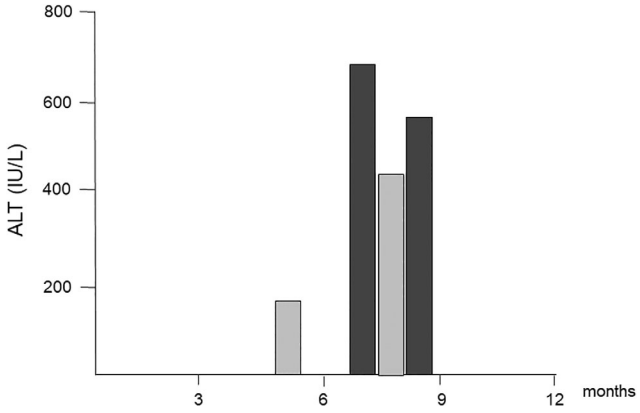

Figure 3 Graphical illustration of hepatitis relapse with elevated alanine aminotransferase serum levels in four patients during follow-up.

dose reduction occurred in four patients (two in each group after a median time of 214 days [149–242], see Fig. 3), which required treatment adjustment to re-induce biological remission.

Weaning from immunosuppressive drugs. Administration of IST, either corticosteroids or any type of IST, in the two groups is illustrated in Figure 3. Compared to the group of classical AIH, more patients in the IMDILI group had been weaned off corticosteroids at the end of follow-up (11/16 [68.7%] *vs* 4/15 [26.6%], $P < 0.02$), with differences being apparent after nearly 6 months of treatment (see Fig. 4). After 1 year of follow-up, there was a tendency toward more patients in IMDILI group compared to classical AIH group being off any type of IST (13/16 [81%] *vs* 15/15 [100%], $P = 0.08$). The three patients in the IMDILI group in whom IST could be stopped during follow-up had been initially exposed to nitrofurantoin, olmesartan, and a natural product.

Discussion

This study describes in detail the characteristics of consecutive patients admitted to hospital with acute hepatitis and biological and histological features suggestive of autoimmune liver injury, some of whom had been recently exposed to a drug. These patients with apparent dual liver diseases (AIH and DILI) seem to behave in a manner slightly different compared to patients with a "classical" form of AIH, with discontinuation of corticosteroids during follow-up being more frequent, together with a tendency to be weaned off any IST.

This observation of patients presenting with acute liver injury associated with both autoimmune and DILI features is in line with the proposed definition of IMDILI, that is, AIH triggered by exposure to a drug that may persist even when the incriminating drug is withdrawn.[10,12] However, on the other hand, any liver injury consequent to exposure to a drug should be considered as DILI, a vast area of hepatology in which any type of liver lesions can be observed.[21] Therefore, it remains challenging to determine whether a patient has an underlying or latent AIH unmasked by the exposure to a drug, or whether he or she is suffering from acute DILI associated with autoimmune manifestations.[9,10] Allergic type of reactions such as fever or rash are seldom reported in IMDILI patients,[5] and the presence of concurrent autoimmune diseases conferring a higher risk of classical AIH is inconsistent.[20] Differentiating classical AIH from IMDILI is, however, clinically relevant with possible impact on the long-term clinical management. Accordingly, weaning and discontinuation of IST during follow-up without disease relapse is more frequent in patients

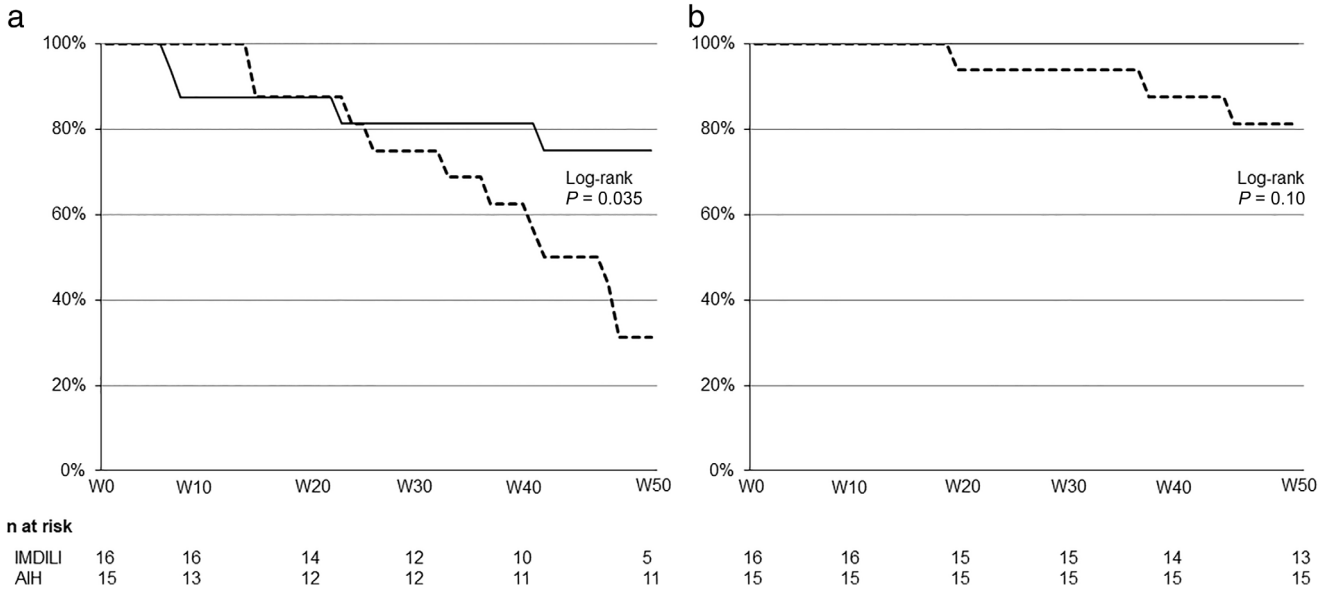

Figure 4 Kaplan–Meier curve with log-rank test illustrating the long-term exposure (in weeks: W) to immunosuppressive drugs in patients with IMDI (dashed line) and in patients with autoimmune hepatitis (full line). (a) Steroids only. (b) Any immunosuppressive treatment. IMDI, immune-mediated drug induced.

diagnosed with IMDILI compared to those with the classical form of AIH, as found in a retrospective study by Björnsson *et al.*[12] Similarly, Licata *et al.*[13] reported a small group of 12 patients with DILI and features of AIH who were able to achieve long-term remission sometimes without the use of steroids. The present study had a similar design using a large database of a tertiary care center including well-characterized patients, detailed baseline liver biopsies, and serological tests. Thus, our results are consistent with the literature and suggest that long-term IST may not be necessary in all patients diagnosed with IMDILI.

Diagnosing AIH may be challenging.[22] The presence of circulating autoantibodies, hypergammaglobulinemia, and the absence of viral hepatitis and chronic active hepatitis on liver biopsy are taken into consideration and incorporated into a probability scale for the diagnosis of AIH.[19] Our patients presented with similar biochemical and serological profiles at hospital admission, and liver biopsy findings showed in both groups histological features suggestive of AIH. Thus, in the absence of specific baseline characteristics, it is very difficult to diagnose IMDILI early in the course of the disease. A recent study identified a particular autoantibody profile as a potential biomarker to distinguish IMDILI from classical AIH.[23] At present, both a careful drug history taken at admission and the clinical and biochemical course during follow-up may suggest a diagnosis of IMDILI. Accordingly, several drugs that our patients have been exposed to have been reported as a possible trigger of IMDILI.[7-9,12,13] We suggest the inclusion of the antidepressant trazodone to the list of potentially harmful compounds. Complementary and alternative medicine agents may also trigger autoimmune-like hepatitis.[15] Both "classical" AIH and IMDILI require the initial administration of prednisolone followed by IST. In our patients, weaning off steroids during follow-up was more frequent in IMDILI patients compared to those in the classical AIH group, together with a trend toward less IST to maintain biochemical remission. Thus, maintenance of IST in the long term may not be necessary in every patient presenting with features of AIH.

Both the striking similarities between AIH and this particular presentation of DILI and the absence of an accurate diagnostic biomarker may together result in an under-reporting of IMDILI as a particular manifestation of hepatotoxicity. The present study on well-characterized patients with features of AIH and close follow-up underlines the importance of taking a detailed history of exposure to a potentially harmful drug in order to suspect a diagnosis of IMDILI. However, we acknowledge that our study suffers from some limitations, including the small number of patients, the retrospective design of the study, and the absence of follow-up beyond 12 months. In addition, although we focused our interest on acute hepatitis resulting from drug-induced immune-mediated injury, the possibility that similar autoimmune injury may affect the bile ducts cannot be ruled out.[24] Future studies are needed to identify biomarkers that are able to diagnose IMDILI early in the course of the disease and predict the risk of hepatitis relapse over time.

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