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ORIGINAL ARTICLE

Setting up criteria for drug-induced autoimmune-like hepatitis through a systematic analysis of published reports

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Abstract

Nitrofurantoin, minocycline, methyldopa and infliximab, have been found to induce autoimmune-like hepatitis (DI-AILH). Evidence for other drugs and herbal and dietary supplements (HDS) is unclear. The aims of the study were to establish criteria to define and review the published evidence of suspected DI-AILH. Search was undertaken in Pubmed using search terms "drug-induced liver injury," "autoimmune hepatitis," and "drug-induced autoimmune hepatitis." DI-AILH was defined as (1) drug as a potential trigger of liver injury with autoimmune features and histological findings compatible with AIH; (2) no or incomplete recovery or worsening of liver tests after discontinuation of the drug; (3) corticosteroids requirement or spontaneous recovery; (4) follow-up without immunosuppression (IS) and no relapse of AIH at least 6 months after discontinuation of IS; and (5) drugs potentially inducing AILH with a chronic course. Cases fulfilling the first four criteria were considered probable DI-AILH with three possible DI-AILH. A total of 186 case reports were identified for conventional drugs (*n* = 148; females 79%; latency 2.6 months) and HDS (*n* = 38; females 50%). The most commonly reported agents of DI-AILH were interferons (*n* = 37), statins (*n* = 24), methylprednisolone (MPS) (*n* = 16), adalimumab (*n* = 10), imatinib (*n* = 8), and diclofenac (*n* = 7). Tinospora cordifolia and Khat were the only HDS with probable DI-AILH cases. No relapses of AIH were observed when IS was stopped after interferons, imatinib, diclofenac, and methylprednisolone. *Conclusion*: Beyond well-recognized nitrofurantoin, methyldopa, hydralazine, minocycline, and infliximab as causes of DI-AILH, interferons, imatinib, adalimumab, and MPS were the best-documented agents leading to probable DI-AILH. Khat and Tinospora cordifolia were the only HDS found to be able to induce DI-AILH. Long-term immunosuppression appears to be rarely required in patients with DI-AILH due to these drugs.

INTRODUCTION

Drug-induced autoimmune-like hepatitis (DI-AILH) is an emerging phenotype of hepatotoxicity traditionally related to a number of specific drugs such as hydralazine, methyldopa, nitrofurantoin, minocycline, and infliximab, and with HDS such as black cohosh.[1–9] There is at the current time no agreement on the definitions.[10,11] Autoantibodies can be found in many liver disorders other than autoimmune hepatitis (AIH), such as acute liver failure,[12] acute *idiosyncratic* DILI,[13,14] liver injury due to HDS,[15] and in chronic liver diseases.[16–18] Thus, autoantibodies are often secondary to liver injury, and it can be difficult to ascertain whether autoimmune mechanisms are involved in the pathogenesis of the liver injury.

In one study, patients with DI-AILH due to nitrofurantoin and minocycline had very similar clinical, immunological, and histological features as those with idiopathic AIH, except lack of relapse after discontinuation of corticosteroids.[5] This has also been seen with hydralazine, methyldopa and infliximab, as liver injury with autoimmune features due to these drugs does not usually relapse after patients enter biochemical remission.[7,19–21] More than 30 drugs have been suspected to lead to DI-AILH, but for many of these drugs, the documented evidence is limited and consists of a single report.[9,22,23]

The terminology used to describe what we have chosen to call DI-AIH is controversial. It has also been called "drug-induced autoimmune-like hepatitis,"[9] "immune-mediated DILI,"[24] and "drug-induced liver injury with autoimmune features."[25] Although drug-induced AIH (DI-AIH) has been most frequently used in recent literature,[5,10,26–28] it is still controversial and we have therefore chosen to name this condition, drug-induced autoimmune-like hepatitis (DI-AILH).

Criteria for DI-AILH have been largely lacking. The aim of the study was to establish a set of criteria to define DI-AILH and to review the literature and analyze the suspected cases of this clinical phenotype following these predefined criteria.

METHODS

Search was undertaken in Pubmed (pubmed.ncbi.nlm.nih.gov) on "drug-induced liver injury," "autoimmune hepatitis," and "drug-induced autoimmune hepatitis" until 2021. References cited in the articles that were identified through the literature search were reviewed to retrieve additional case reports.

Published case reports and case series on DI-AILH were analyzed. Case reports with drugs or HDS suspected to have induced AIH-like picture were reviewed and the following information obtained: age, gender, suspected drug or HDS, duration of drug therapy, antinuclear antibodies (ANAs), anti-smooth muscle antibodies (SMAs), IgG levels, liver biopsy, and whether the histology was compatible with AIH. From these results, the new simplified score for AIH was calculated.[29] Liver biopsy results were registered in accordance with the Hennes et al. paper.[29] Information was also obtained on whether drug discontinuation led to improvement in liver tests or whether there was incomplete recovery after discontinuation of the implicated drug. Information was registered on the use of corticosteroids and other immunosuppressive therapies (IS). Information on the dose of corticosteroids was often missing, and when it was provided it was very heterogeneous in the different case reports and seemed to be according to the standard of care for use in idiopathic AIH. Importantly, whether IS had been discontinued, and if the patient had experienced a relapse, and what the duration of follow-up was in months, was determined. Patients who were still on IS at the time of the case report were not excluded, but the case could only be according to our definition a possible DI-AILH. In other words, they lacked complete documentation that provided evidence of a probable DI-AILH. References from all case reports that were analyzed are in found in the Supporting Information.

DI-AILH was defined as follows:

1. Drug as a potential trigger of liver injury with autoimmune features and histological findings compatible with AIH: elevation in any of ANAs, SMAs and IgG, and a liver biopsy compatible with AIH, as stated in the paper by Hennes et al. on the new simplified criteria (NSC).[29] Thus, it was not enough to have either positive ANA/SMA/IgG or a liver biopsy compatible with AIH.
2. No or incomplete recovery or worsening of liver tests after discontinuation of the drug.
3. Corticosteroids requirement for or spontaneous recovery of AIH. Although there was in some cases spontaneous recovery, it was prolonged, taking many weeks (not contradicting criteria 2).
4. Follow-up without IS and no relapse of AIH at least 6 months after discontinuation of IS.
5. Drugs potentially inducing AILH with a chronic course

Published clinical case reports with at least two convincing reports fulfilling three of the first four criteria were considered possible DI-AILH, and all four criteria as probable DI-AILH. Relapse of AIH was analyzed after discontinuation of IS when that was tried. DI-AILH due to nitrofurantoin, methyldopa, hydralazine, minocycline, and infliximab was excluded, as was liver injury associated with immune checkpoint inhibitors.

RESULTS

A total of 186 case reports were identified for conventional drugs (n = 148) and HDS (n = 38).

The most commonly reported class of agents leading to DI-AILH were interferons, (*n* = 39), statins (*n* = 24), methylprednisolone (*n* = 16), imatinib (*n* = 10), adalimumab (*n* = 10), and diclofenac (*n* = 7). Drugs included two cases, efalizumab and etanercept, and 38 reports with single reports or more but not fulfilling the criteria of DI-AILH in at least two reports.

Interferons

A total of 39 case reports with interferon-induced liver injury were retrieved; two were excluded due to the lack of data (Supporting Information [SI] 1 and 2), but 17 publications contained 37 case reports (SI 3–19). Females made up 32 of 37 (86%); median age of 38 years (range 11–68) (Table 1). Indications for interferon alpha was hepatitis non-A, non-B, hepatitis C (*n* = 14) and interferon beta, indication multiple sclerosis (*n* = 23). The median duration of interferon therapy was 3 months. In none of the reports from 1989 to 2004, discontinuation of IS was attempted (Table 1). Since 2006, when IS was reported to have been stopped, all of that were tried (*n* = 8) were successful (Table 1). Thus, eight cases of interferon fulfilled all criteria for probable DI-AILH (Table 1). In none of the case reports was there a relapse after patients entered biochemical remission, and therefore did not fulfill criteria 5 of being able to induce chronic self-perpetuating AIH.

Statins

A total of 24 cases of statin DI-AILH were retrieved (SI 20–31), which consisted mostly of atorvastatin (*n* = 11) (Table 2). Females made up 67% of the patients (median age 58 years and 4 months duration [range 1.5–62 months]). Relapse after corticosteroids discontinuation was commonly observed (*n* = 7). Only 4 of 24 (17%) fulfilled the criteria for probable DI-AIH-like (Table 2). A total of seven case reports of statin-induced DI-AILH phenotype fulfilled criteria 5, suggesting that statins might trigger classical AIH, with atorvastatin (*n* = 3), simvastatin (*n* = 3) and rosuvastatin (Table 2).

Imatinib and other kinase inhibitors

A total of eight cases with imatinib were reported (6 females [75%; SI 32–39]; median age of 57 years [range 27–68]; and 3 months duration of therapy) (Table 3). None of the patient who discontinued corticosteroids had relapse of DI-AILH. Masitinib and pazopanib seemed to cause a similar DI-AILH (Table 3). In none of the case reports was there a relapse reported after patients entered biochemical remission, and therefore did not fulfill criteria 5 of being able to trigger classical AIH.

Adalimumab, etanercept, and efalizumab

In 10 case reports adalimumab was believed to have induced DI-AILH (SI 39–46). A total of 9 of 10 (90%) were female (median age of 43 years; 3 months of therapy) (Table 4). Most patients continued on corticosteroids, but in 2 of 3 patients no relapse was observed after stopping immunosuppression. Convincing cases of DI-AILH were found to be associated with etanercept and efalizumab (SI 47–49), but in all of these patients corticosteroid therapy was maintained (Table 4). One patient had a mild relapse (SI 45), and it is conceivable that adalimumab might trigger or induce classic AIH, as it fulfilled criteria 5 in this case.

Diclofenac

Seven patients were suspected of DI-AILH (Table 5). All except 1 was from the early 1990s and based on only three reports (SI 29 and 50–51). Most were female (median age of 46 years; 2.5 months of therapy). In 4 of these patients with autoimmune features, corticosteroids were required; and in 3 of these patients. corticosteroids were discontinued without evidence of relapse. In none of the case reports was there a relapse after patients entered biochemical remission.

Methylprednisolone

Methylprednisolone (MPS) given intravenously in high pulses has been associated with liver injury with autoimmune features, and a total 16 cases were retrieved (SI 52–55). Most (94%) were of female gender. IS was stopped in 13 of 16 (81%) patients, and none of these patients were found to experience a relapse of DI-AILH (Table 6). In none of the case reports was there a relapse after patients entered biochemical remission, and MPS was not reported to induce AIH phenotype with a chronic course.

Herbal and dietary supplements

Only four different agents were retrieved: germander, black cohosh, khat, and Tinospora cordifolia (SI 56–62). None of the reports with suspected of DI-AILH due to germander (56) and black cohosh (SI 57 and 58) fulfilled the criteria for probable DI-AILH (Table 7). Two reports with turmeric were identified (SI 59 and 60) that

TABLE 1 Suspected DI-AILH associated with interferons

	Age, years/ gender, F/M	Drug	Duration (months)	ANA	SMA	IgG high	Biopsy	Cortico-steroids	Other IS	Relapse	NSC	F-U	Still on IS	Criteria for DI-AILH
Vento 1989 (SI 3)	49/F	Interferon alfa	1	Pos	Pos	Yes	Yes	Yes	Pos	No	8	6	Yes	1,2,3
Vento 1989 (SM 3)	17/M	Interferon alfa	1.5	Pos	Neg	Yes	Yes	Yes	Yes	No	7	24	Yes	1,2,3
Silva 1991 (SI 4)	54/M	Interferon alfa	4	Pos	Pos	N/A	Yes	Yes	No	No	5	6	Yes	1,2,3
Ruiz- Moreno 1991 (SI 5)	11/F	Interferon alfa	3	Pos	Neg	Yes	No	Yes	Yes	No	5	4	Yes	1,2,3
Shindo 1992 (SI 6)	68/M	Interferon alfa	0,5	Pos	Neg	N/A	Yes	Yes	No	No	4	–	Yes	1,2,3
Papo 1992 (SI 7)	20/M	Interferon alfa	3	Pos	Pos	Yes	Yes	Yes	No	No	6	–	Yes	1,2,3
Papo 1992 (SI 7)	40/F	Interferon alfa	1	Pos	Pos	No	Yes	Yes	No	No	5	–	Yes	1,2,3
Papo 1992 (SI 7)	42/F	Interferon alfa	1	Pos	Pos	Yes	Yes	Yes	No	No	6	–	Yes	1,2,3
Garcia- Buey 1995 (SI 8)	39/F	Interferon alfa	N/A	Pos	Pos	Yes	Yes	Yes	No	No	–	–	Yes	1,2,3
Garcia- Buey 1995 (SI 8)	34/F	Interferon alfa	N/A	Pos	Pos	Yes	Yes	Yes	No	No	–	–	Yes	1,2,3
Garcia- Buey 1995 (SI 8)	22/F	Interferon alfa	N/A	Pos	Pos	Yes	Yes	Yes	No	No	–	–	Yes	1,2,3
Garcia- Buey 1995 (SI 8)	39/F	Interferon alfa	N/A	Pos	Pos	Yes	Yes	Yes	No	No	–	–	Yes	1,2,3
Garcia- Buey 1995 (SI 8)	60/F	Interferon alfa	N/A	Pos	Pos	Yes	Yes	Yes	No	No	–	–	Yes	1,2,3
Garcia- Buey 1995 (SI 8)	45/F	Interferon alfa	N/A	Pos	Pos	Yes	Yes	Yes	No	No	–	–	Yes	1,2,3
Durelli 1998 (SI 9)	27/F	Interferon beta	4.5	Pos	Pos	No	No	Yes	No	No	3	[a]	Yes	4
Durelli 1998 (SI 9)	24/F	Interferon beta	2	Pos	Pos	N/A	No	No	No	No	3	2	No	4
Yoshida 2001 (SI 10)	59/F	Interferon beta	2	Neg	Neg	N/A	Yes	Yes	No	No	2	–	Yes	1,2,3
Duchini 2002 (SI 11)	38/F	Interferon beta	24	Pos	Pos	Yes	Yes	Yes	Yes	No	7	–	Yes	1,2,3
Wallack 2004 (SI 12)	52/F	Interferon beta	24	Pos	Pos	N/A	No	Yes	No	No	4	–	Yes	1,2,3
Byrnes 2006 (SI 13)	37/F	Interferon beta	10	Pos	Pos	Yes	Yes	Yes	No	No	6	10	No	1,2,3,4
Byrnes 2006 (SI 13)	37/F	Interferon beta	8	Neg	Neg	Yes	Yes	Yes	Yes	No	5	–	Yes	1,2,3

TABLE 1 (Continued)

	Age, years/ gender, F/M	Drug	Duration (months)	ANA	SMA	IgG high	Biopsy	Cortico-steroids	Other IS	Relapse	NSC	F-U	Still on IS	Criteria for DI-AILH
Byrnes 2006 (SI 13)	30/F	Interferon beta	2	Pos	Pos	No	Yes	No	No	No	5	–	No	1,2,3,4
Pulicken 2006 (SI 14)	43/F	Interferon beta	1,5	Pos	Pos	N/A	Yes	Yes	Yes	No	5	7	No	1,2,3,4
Montero 2007 (SI 15)	39/F	Interferon beta	60	Pos	Pos	N/A	Yes	Yes	No	No	5	–	Yes	1,2,3
Kowalec 2014 (SI 16)	42/F	Interferon beta	34	Pos	N/A	N/A	No	No	No	No	4	7	No	1,2,4
Villamil 2014 (SI 17)	20/F	Interferon beta	0,75	Neg	Pos	No	Yes	Yes	Yes	No	4	36	No	1,2,3,4
Villamil 2014 (SI 17)	47/M	interferon beta	1	Pos	Neg	No	Yes	Yes	Yes	No	4	36	No	1,2,3,4
Kalafateli 2016 (SI 18)	57/F	Interferon beta	24	Pos	Pos	No	Yes	No	No	No	6	36	No	1,2,3,4
Rigopoulou 2018 (SI 19)	38/F	Interferon beta	11	Pos	Pos	No	Yes	Yes	Yes	No	5	–	Yes	1,2,3
Rigopoulou 2018 (SI 19)	34/F	Interferon beta	312	Pos	Pos	N/A	Yes	Yes	Yes	No	5	72	No	1,2,3,4
Rigopoulou 2018 (SI 19)	57/F	Interferon beta	24	Neg	Pos	N/A	Yes	Yes	Yes	No	5	–	Yes	1,2,3
Rigopoulou 2018 (SI 19)	34/F	Interferon beta	3	Pos	Pos	N/A	Yes	Yes	Yes	No	5	–	Yes	1,2,3
Rigopoulou 2018 (SI 19)	38/F	Interferon beta	1	Neg	Pos	N/A	Yes	Yes	Yes	No	5	104	No	1,2,3,4
Rigopoulou 2018 (SI 19)	31/F	Interferon beta	12	Pos	Pos	N/A	Yes	Yes	Yes	No	5	–	Yes	1,2,3
Rigopoulou 2018 (SI 19)	36/F	Interferon beta	84	Neg	Pos	N/A	Yes	Yes	Yes	No	5	–	Yes	1,2,3
Rigopoulou 2018 (SI 19)	35/F	Interferon beta	2	Pos	Pos	N/A	Yes	Yes	Yes	No	5	–	Yes	1,2,3
Rigopoulou 2018 (SI 19)	37/F	Interferon beta	3	Neg	Pos	N/A	Yes	Yes	Yes	No	5	–	Yes	1,2,3

Abbreviations: ANA, antinuclear antibody; DI-AILH, drug-induced autoimmune-like hepatitis; F, female; F-U, follow-up; IS, immunosuppression; M, male; N/A, not available; Neg, negative; NSC, new simplified criteria for AIH (Ref. 29); Pos, positive; SI, Supporting Information; SMA, smooth muscle antibody.

[a]Lethal acute liver failure.

TABLE 2 Suspected DI-AILH associated with statins

	Age, years/ gender, F/M	Drug	Duration (months)	ANA	SMA	IgG high	Biopsy	Cortico-steroids	Other IS	Relapse	NSC	F-U	Still on IS	Criteria for DI-AILH
Graziadei 2003 (SI 20)	58/F	Atorvastatin	7	Pos	Neg	Yes	Yes	Yes	Yes	Yes	6	12	Yes	1,2,3
Pelli 2003 (SI 21)	65/F	Atorvastatin	3	Pos	Pos	Yes	Yes	Yes	No	No	7	3	Yes	1,2,3
Wolters 2005 (SI 22)	46/F	Rosuvastatin	2	Neg	Pos	–	Yes	Yes	No	–	6	6	Yes	1,2,3
Alla 2006 (SI 23)	51/F	Simvastatin	4	Pos	Pos	Yes	Yes	Yes	Yes	Yes	7	36	Yes	1,2,3
Alla 2006 (SI 23)	47/M	Atorvastatin	4	Pos	Neg	No	Yes	Yes	Yes	No	5	24	Yes	1,2,3
Alla 2006 (SI 23)	51/M	Atorvastatin	4	Pos	Pos	Yes	Yes	Yes	Yes	–	7	6	Yes	1,2,3
Lucena 2011 (SI 24)	51/F	Fluvastatin	3	Pos	Pos	Yes	Yes	No	No	No	7	12	No	1,2,4
Russo 2009 (SI 25)	52/F	Atorvastatin	2	Pos	Pos	Yes	Yes	Yes	Yes	Yes	6	-	Yes	1,2,3
Russo 2014 (SI 26)	71/M	Atorvastatin	42	Pos	Pos	Yes	Yes	Yes	No	No	7	12	Yes	1,2,3
Russo 2014 (SI 26)	61/F	Atorvastatin	62	Pos	–	–	–	Yes	Yes	No	7	20	No	1,2,3,4
Russo 2014 (SI 26)	75/F	Fluvastatin	37	–	–	–	–	–	–	–	–	10	Yes	1,2,3
Russo 2014 (SI 26)	53/F	Pravastatin	12	–	–	–	–	–	–	–	–	–	–	1,2,4
Russo 2014 (SI 26)	58/F	Rosuvastatin	3	Pos	Pos	Yes	Yes	Yes	No	Yes	–	–	–	1,2,4
Russo 2014 (SI 26)	43/M	Simvastatin	7	–	–	–	–	–	–	–	7	11	Yes	1,2,3
Perdices 2014 (SI 27)	67/F	Atorvastin	3	Pos	Pos	Yes	Yes	No	No	No	8	36	No	1,2,4
Perdices 2014 (SI 27)	63/M	Atorvastin	24	Pos	N/A	N/A	No	No	No	No	4	7	No	1,2,4
Perdices 2014 (SI 27)	67/F	Simvastatin	2	Pos	Pos	No	Yes	Yes	Yes	Yes	5	2	No	1,2,3,4
Perdices 2014 (SI 27)	67/M	Fluvastatin	4	Pos	Neg	Yes	Yes	Yes	Yes	No	6	96	No	1,2,3,4
Sanchez 2018 (SI 28)	47/M	Rosuvastin	11	Pos	Pos	No	No	No	No	No	4	12	No	1,2,4
Yeong 2016 (SI 29)	63/F	Simvastatin	18	Pos	N/A	N/A	Yes	Yes	Yes	No	–	–	Yes	1,2,3
Yeong 2016 (SI 29)	69/F	Simvastatin	36	Pos	N/A	N/A	Yes	Yes	No	Yes	–	16	Yes	1,2,3
Yeong 2016 (SI 29)	78/F	Atorvastatin	19	Pos	N/A	N/A	Yes	Yes	No	Yes	–	36	Yes	1,2,3
Shah 2019 (SI 30)	47/M	Rosuvastin	1,5	Neg	Neg	No	Yes	Yes	No	No	2	12	No	1,2,3,4
Khan 2020 (SI 31)	57/F	Atorvastatin	3	Pos	Pos	No	No	No	No	No	3	18	No	1,2,4

TABLE 3 Suspected DI-AILH associated with imatinib, mastinib, and pazopanib

	Age, years/ gender, F/M	Drug	Duration (months)	ANA	SMA	IgG high	Biopsy	Cortico-steroids	other IS	Relapse	NSC	F-U	Still on IS	Criteria for DI-AILH
Dhalluin-Venier 2006 (SI 32)	18/F	Imatinib	0.5	Neg	Neg	Yes	Yes	Yes	No	No	5	11	Yes	1,2,3
Al Sobhi 2007 (SI 33)	17/F	Imatinib	18	Pos	Pos	Yes	Yes	Yes	No	No	7	12	No	1,2,3,4
Aliberti 2009 (SI 34)	65/M	Imatinib	1	Pos	Neg	N/A	Yes	Yes	No	No	4	12	No	1,2,3,4
Charier 2009 (SI 35)	46/F	Imatinib	4	Pos	Neg	Yes	Yes	Yes	Yes	No	7	–	Yes	1,2,3
Björnsson 2017 (SI 36)	60/F	Imatinib	6	Pos	Neg	No	Yes	Yes	No	No	4	60	No	1,2,3,4
Kang 2019 (SI 37)	55/M	Imatinib	10	Neg	Neg	No	Yes	Yes	No	No	4	–	–	2,3
Ayoub 2005 (SI 38)	22/F	Imatinib	1	Pos	Neg	No	Yes	No	No	No	5	3	No	1,2,4
Spanish DILI Reg	61/F	Imatinib	5	Neg	Neg	No	Yes	Yes	No	No	3	28	No	2,3,4
Spanish DILI Reg	58/M	Masitinib	1	Pos	Neg	N/A	No	No	No	No	5	8	No	1,2,3,4
LATINDILIN	68/M	Pazopanib	1,5	Neg	Neg	N/A	No	Yes	No	No	3	6	No	2,3,4

Abbreviations: LATINDILIN, Latin American DILI Network; Spanish DILI Reg, Spanish DILI registry.

were (according to the criteria) possible DI-AILH, which recovered relatively quickly after discontinuation of turmeric and did not require corticosteroids. Drawbacks of the case reports were lack of exclusion of hepatitis E (SI 59) and a very short follow-up (SI 60).

A total of 11 reports associated with khat (all males) were identified (SI 61 and 62). In a case series (SI 61), three cases fulfilled the criteria for probable DI-AILH. One patient had only 3 months of follow-up (Table 7).

In two recent papers from India (SI 63 and 64), Tinospora cordifolia was associated with liver injury with prominent autoimmune features in a total of eight cases (7 women) (Table 7). Three cases fulfilled the criteria for probable DI-AILH associated with Tinospora cordifolia. In only one of the case reports of HDS with at least two convincing cases reported was there a relapse after patients entered biochemical remission, which was in a case report with black cohosh (SM57), which fulfilled criteria 5 of being able to induce chronic self-perpetuating AIH.

A variety of different HDS have been associated with DI-AILH in single cases, such as Dai-saiko-to, Ma Huang, N-nitroso-fenfluramine, glucosamine/chondroitin, echinacea, camellia sinensis, and Xiang-tian-guo (SI 65–71). In none of these reports did cases of probable DI-AILH fulfill the criteria (data not shown).

Other case reports

Many drugs have been reported to have induced AIH-like phenotype. These were reported as early as 1971 until 2021. The following drugs were implicated with one or two reports, but not fulfilling criteria for DI-AILH for at least two cases, with a total of 38 case reports: oxyphenisatin (n = 7), sulfamethoxypyridazin, propylthiouracil (n = 2), dantrolene, perhexiline, clometacin (n = 2), amiodarone, pemoline (n = 2), meloxicam, moxifloxacin, omeprazole, ezetimibe/enalapril, olanzapine, metotrexate, bosentan, camostat/benzbromarone, papaverin, benzarone, terbinafine, methylphenidate, bupropion, indomethacin, enalapril/metformin, olmesartan/amlodipine, varenicline, menotrophin, and cyproterone acetate (n = 2) (SI 24 and 72–97). During the early part of the study period, hepatitis C serology was not available, which made interpretation of the case reports more difficult and lead to exclusion of cases such as for oxyphenisatin.

Most of the single reports lacked important elements to evaluate for DI-AILH or were unconvincing. In many of these patients, autoantibodies, ANAs, and/or SMAs disappeared after the implicated drug had been discontinued (data not shown). Among these 27 drugs (a few drug combinations), only one fulfilled the criteria for probable DI-AILH, which was cyproterone acetate in one out of two reports (SI 97). Thus, despite many reports with single or two reports of the same drug, the

TABLE 4 Suspected DI-AILH associated with reports with adalimumab, etanercept, and efalizumab

	Age, years/ gender, F/M	Drug	Duration (months)	ANA	SIA	IgG high	Biopsy	Cortico-steroids	Other IS	Relapse	NSC	F-U	Still on IS	Criteria for DI-AILH
Grasland 2012 (SI 39)	35/F	Adalimumab	2.5	Pos	Pos	Yes	Yes	Yes	Yes	No	7	8	No	1,2,3,4
Lucena 2011 (SI 24)	47/F	Adalimumab	1.5	Pos	Neg	No	N/A	No	No	No	3	6	No	1,2,4
Adar 2010 (SI 40)	36/F	Adalimumab	3	Pos	Neg	Yes	Yes	Yes	Yes	No	7	5	Yes	1,2,3
Nakayama 2013 (SI 41)	52/F	Adalimumab	2	Pos	Neg	Yes	Yes	Yes	No	No	7	–	–	–
Petriková 2015 (SI 42)	33/F	Adalimumab	1.5	Pos	Pos	Yes	Yes	Yes	No	No	7	–	–	–
Rodrigues 2015 (SI 43)	45/F	Adalimumab	N/A	Pos	Neg	Yes	Yes	Yes	Yes	No	7	–	–	–
Miranda- Bautista 2019 (SI 44)	54/M	Adalimumab	6	Pos	Neg	N/A	Yes	No	No	No	6	36	No	1,4
Rösner 2013 (SI 45)	37/F	Adalimumab	9	Neg	Neg	No	Yes	Yes	No	Yes	3	84	Yes	2,3
Rösner 2013 (SI 45)	41/F	Adalimumab	60	Pos	Pos	No	Yes	Yes	No	No	5	96	No	1,2,3,4
Rösner 2013 (SI 45)	52/F	Adalimumab	12	Pos	Neg	No	Yes	No	No	No	5	6	No	1,2,4
Titos- Arcos 2012 (SI 46)	47/F	Adalimumab	2	Pos	Neg	No	No	No	No	No	5	24	No	1,4
Fathalla 2008 (SI 47)	9/F	Etanercep	10	Pos	Pos	Yes	Yes	Yes	Yes	No	7	3	Yes	1,2,3
Harada 2008 (SI 48)	50/F	Etanercep	0,5	Pos	Pos	Yes	Yes	Yes	No	No	7	28	Yes	1,2,3
Primo 2010 (SI 49)	55/F	Efalizumab	20	Pos	Pos	Yes	Yes	Yes	Yes	No	7	8	Yes	1,2,3
Spanish DILI Reg	56/F	Efalizumab	2,6	Pos	Neg	Yes	Yes	Yes	No	No	–	6	Yes	1,2,3

TABLE 5 Suspected DI-AILH associated with diclofenac

	Age, years/ gender, F/M	Drug	Duration (months)	ANA	SMA	IgG high	Biopsy	Cortico-steroids	Other IS	Relapse	NSC	F-U	Still on IS	Criteria for DI-AILH
Sallie 1991 (SI 50)	72/M	Diclofenac	1.5	Pos	Pos	N/A	Yes	No	No	No	5	6	No	1,2,4
Sallie 1991 (SI 50)	74/M	Diclofenac	4	Pos	Pos	N/A	Yes	No	No	No	5	3	No	1,2,4
Sallie 1991 (SI 50)	76/F	Diclofenac	2	Neg	Pos	N/A	Yes	Yes	No	No	4	48	No	1,2,3,4
Scully 1993 (SI 51)	69/F	Diclofenac	4	Pos	Neg	No	Yes	Yes	No	No	4	16	No	1,2,3,4
Scully 1993 (SI 51)	57/F	Diclofenac	3	Pos	Neg	No	Yes	Yes	No	No	4	12	No	1,2,3,4
Scully 1993 (SI 51)	48/F	Diclofenac	2	Pos	Neg	No	Yes	No	No	No	4	7	No	1,2,4
Yeong 2016 (SI 29)	19/F	Diclofenac	2	Pos	N/A	N/A	Yes	Yes	Yes	No	5	–	Yes	1,2,3

association between drug intake and development of autoimmune features was in most cases unconvincing, and in some cases this was due to lack of important data.

Table 8 lists the clinical characteristics of DI-AILH cases according to the therapeutic class of culprit compounds. The mean duration of therapy before detection of elevated liver tests was 2.6 months, and most of those with DI-AILH due to conventional drugs were of female gender (79%). Liver biopsy was undertaken in most cases, and corticosteroids were used for the liver inflammation in most cases (Table 8).

DISCUSSION

The results of the current study demonstrate that mostly drugs that are immune modulators or affect the immune system such as interferon, imatinib, adalimumab, and methylprednisolone had convincing reports of DI-AILH. Statins and diclofenac were found to a lesser extent to have reports that appear to induce DI-AILH. Primarily statins were found to be suspected to trigger classical AIH, which was not seen with the other drugs with an exception of one case with adalimumab. In terms of HDS, khat and—more recently—Tinospora cordifolia appear to be able to induce DI-AILH. However, most single reports with a number of drugs and HDS that were suggested to cause DI-AILH were found to be unconvincing and lacked evidence of a relationship between the drugs as the etiology of abnormal liver tests with autoimmune features. Unfortunately, the current study does not answer the question of why these particular drugs induce in some patients an AIH-like pattern, which in most cases required corticosteroids and very rarely relapsed after stopping immunosuppression.

The major diagnostic challenge in the diagnosis of DI-AILH is to assign an etiological role of a specific drug. This issue has not only implications in the clinical scenario but also in drug development. Drugs that have been well documented to induce liver injury with autoimmune features as mentioned previously are methyldopa, nitrofurantoin, hydralazine, and minocycline.[2,5,9,19,30,31] All of these drugs have a well-recognized ability to cause DILI in general, all of whom with more than 100 reports of liver injury.[32] Recently, infliximab has been shown to cause liver injury with autoimmune features.[7,33] Thus, there appears to be little doubt that methyldopa, nitrofurantoin, hydralazine, minocycline, and infliximab can lead to DI-AILH[2,5,7,9,17,30,31] and were therefore not included in the current study. Furthermore, liver injury associated with immune checkpoint inhibitors was not included in the current study, as hepatotoxicity due to these agents is very rarely associated with autoimmune features and the histological injury is not reminiscent of idiopathic autoimmune hepatitis, and therefore appear to be in a separate category.[34] Accordingly, the recent

TABLE 6 Suspected DI-AILH associated with methyprednisolone

	Age, years/ gender, F/M	Drug	Duration (months)	ANA	SMA	IgG high	Biopsy	Cortico-steroids	Other IS	Relapse	NSC	F-U	Still on IS	Criteria for DI-AILH
Salvi 2004 (SI 52)	43/F	MPS	1.5	Pos	Neg	No	Yes	Yes	No	No	4	2.5	Yes	1,2,3
Takahashi 2008 (SI 53)	43/F	MPS	0.5	Pos	Pos	No	Yes	Yes	No	No	5	3	Yes	1,2,3
Nociti 2018 (SI 54)	24/F	MPS	0.5	Neg	Pos	No	Yes	No	No	No	5	6	No	1,2,3,4
Nociti 2018 (SI 54)	19/F	MPS	0.5	Pos	Pos	Yes	Yes	Yes	Yes	No	5	3	Yes	1,2,3
Allgeier 2021 (SI 55)	48/M	MPS	1.5	Pos	Neg	No	Yes	Yes	No	No	5	9	No	1,2,3,4
Allgeier 2021 (SI 55)	26/F	MPS	1.5	Pos	Neg	No	Yes	Yes	No	No	5	52	No	1,2,3,4
Allgeier 2021 (SI 55)	74/F	MPS	0.5	Pos	Neg	No	Yes	No	No	No	5	–	No	–
Allgeier 2021 (SI 55)	49/F	MPS	1.0	Pos	Neg	No	Yes	Yes	No	No	5	26	No	1,2,3,4
Allgeier 2021 (SI 55)	51/F	MPS	1	Pos	Neg	No	Yes	Yes	No	No	5	–	No	–
Allgeier 2021 (SI 55)	23/F	MPS	0,5	Pos	Neg	No	No	No	No	No	4	–	No	2,3,4
Allgeier 2021 (SI 55)	29/F	MPS	0.5	Pos	Neg	No	No	No	No	No	4	14	No	2,3,4
Allgeier 2021 (SI 55)	51/F	MPS	1,9	Pos	Neg	No	No	Yes	No	No	4	–	No	2,3,4
Allgeier 2021 (SI 55)	35/F	MPS	0.5	Pos	Neg	No	No	No	No	No	4	–	No	2,3,4
Allgeier 2021 (SI 55)	35/F	MPS	1.2	Pos	Neg	No	Yes	Yes	No	No	5	–	No	–
Allgeier 2021 (SI 55)	43/F	MPS	0.7	Pos	Neg	No	Yes	Yes	No	No	5	–	No	–
Allgeier 2021 (SI 55)	20/F	MPS	1.8	Pos	Neg	No	Yes	Yes	No	No	5	7	No	1,2,3,4

Abbreviation: MPS, methylprednisolone.

TABLE 7 Suspected DI-AILH associated with HDS

	Age, years/ gender, F/M	Drug	Duration (months)	ANA	SIA	IgG high	Biopsy	Cortico-steroids	Other IS	Relapse	NSC	F-U	Still on IS	Criteria for DI-AILH
Ben Yahia 1993 (SI 56)	37/F	Germander	0,75	Neg	Pos	N/A	Yes	No	No	No	4	16	No	1,2,4
Ben Yahia 1993 (SI 56)	45/F	Germander	6	Pos	Pos	N/A	Yes	No	No	No	4	3	No	1,2,4
Cohen 2004 (SI 57)	57/F	Black kohosh	0.75	Pos	Neg	N/A	Yes	Yes	Yes	Yes	5	–	Yes	1,2,3
Guzman 2009 (SI 58)	42/F	Black kohosh	6	Pos	Pos	N/A	Yes	Yes	Yes	No	5	40	Yes	1,2,3
Guzman 2009 (SI 58)	53/F	Black kohosh	12	Neg	Neg	N/A	Yes	Yes	No	No	4	1.2	Yes	1,2,3
Riyaz 2014 (SI 59)	–/M	Khat	N/A	Neg	Neg	Yes	Yes	Yes	Yes	No	5	1	Yes	1,2,3
Riyaz 2014 (SI 59)	–/M	Khat	N/A	Neg	Neg	No	Yes	Yes	No	No	3	1	Yes	2,3
Riyaz 2014 (SI 59)	–/M	Khat	N/A	Pos	N/A	Yes	Yes	Yes	Yes	No	7	–	Yes	1,2,3
Riyaz 2014 (SI 59)	–/M	Khat	N/A	Pos	N/A	Yes	Yes	Yes	No	No	6	–	Yes	1,2,3
Riyaz 2014 (SI 59)	–/M	Khat	N/A	Pos	N/A	Yes	No	Yes	No	No	5	–	–	–
Riyaz 2014 (SI 59)	–/M	Khat	N/A	Neg	Neg	Yes	Yes	Yes	No	No	5	–	–	–
Teisen 2016 (SI 60)	35/M	Khat	N/A	Neg	Pos	Yes	Yes	Yes	Yes	No	6	3	No	1,2,3,4
Teisen 2016 (SI 60)	38/M	Khat	N/A	Neg	Pos	Yes	Yes	Yes	Yes	No	6	28	No	1,2,3,4
Teisen 2016 (SI 60)	26/M	Khat	N/A	Neg	Pos	Yes	Yes	Yes	Yes	No	6	8	No	1,2,3,4
Teisen 2016 (SI 60)	24/M	Khat	N/A	Neg	Neg	Yes	Yes	Yes	Yes	No	6	6	Yes	1,2,3
Teisen 2016 (SI 60)	52/M	Khat	N/A	Neg	Pos	Yes	Yes	Yes	Yes	No	6	6	Yes	1,2,3
Nagral 2021 (SI 61)	54/F	Tinospora cordifolia	7	Pos	Neg	No	Yes	Yes	No	No	5	12	No	1,2,3,4
Nagral 2021 (SI 61)	38/M	Tinospora cordifolia	6	Pos	Neg	No	Yes	No	No	No	5	8	No	1,4
Nagral 2021 (SI 61)	62/F	Tinospora cordifolia	1	Pos	Pos	N/A	Yes	Yes	No	No	5	12	Yes	1,2,3[a]
Nagral 2021 (SI 61)	56/F	Tinospora cordifolia	0,75	Neg	Neg	Yes	Yes	Yes	No	No	5	12	No	1,2,3,4
Nagral 2021 (SI 61)	56/F	Tinospora cordifolia	3	Neg	Neg	Yes	Yes	No	No	No	5	2	No	1,4
Sahney 2021 (SI 62)	49/F	Tinospora cordifolia	2,8	Pos	Neg	Yes	Yes	Yes	No	No	7	6	No	1,2,3,4
Sahney 2021 (SI 62)	36/F	Tinospora cordifolia	2	Neg	Neg	Yes	Yes	No	No	No	5	3	No	1,4
Sahney 2021 (SI 62)	68/F	Tinospora cordifolia	2,4	Pos	Neg	Yes	Yes	Yes	No	No	5	4	Yes	1,2,3

Abbreviation: HDS, herbal and dietary supplements.

[a]Developed primary sclerosing cholangitis.

(Continues)

TABLE 8 Clinical characteristics of DI-AILH cases according to the therapeutic class of culprit compounds

	Statins	Interferons	Imatinib and other kinase inhibitors	Adalimumab, etanercept, and efalizumab	Diclofenac	Methylprednisolone	HDS
N	24	37	10	15	7	14	24
Fulfilling all four criteria for DI-AIH-like, *n* (%)	4 (17)	8 (22)	4 (40)	2 (13)	3 (43)	5 (36)	6 (25)
Median age, years (range)	59 (43–78)	39 (11–68)	47 (17–68)	43 (9–56)	59 (19–76)	41 (20–74)	46 (24–68)
Female, *n* (%)	16 (67)	32 (86)	6 (60)	14 (93)	5 (71)	15 (94)	12 (50)
Duration of treatment months, median (range)	4 (1.5–62)	3 (0.5–312)	2.8 (0.5–18)	2.8 (0.5–60)	2 (1.5–4)	1 (0.5–1.9)	2.8 (0.75–12)
Positive ANA, *n* (%)	19 (90)	29 (78)	6 (60)	14 (93)	6 (86)	15 (94)	11 (46)
Positive SMA, *n* (%)	12 (75)	30 (83)	1 (10)	6 (40)	3 (50)	2 (13)	8 (38)
IgG > ULN, *n* (%)	11 (68)	14 (70)	3 (42)	9 (64)	0	0	15 (83)
Liver biopsy, *n* (%)	17 (85)	23 (82)	8 (80)	13 (92)	7 (100)	12(75)	23 (96)
Corticosteroids, *n* (%)	16 (76)	33 (89)	8 (80)	11 (73)	4 (57)	12 (75)	19 (79)
Other IS, *n* (%)	9 (43)	17 (46)	1 (10)	5 (36)	1 (14)	0	9 (38)
Relapse, *n* (%)	7 (38)	0	0	1 (7.7)	0		
0	1 (4)						
Time of follow-up months, mean	19	27	18	26	15	16	6
Still on IS, *n* (%)	12 (57)	24 (70)	2 (22)	6 (50)	1 (14)	2 (14)	11 (52)

Abbreviation: ULN, upper limit of normal.

American guidelines on AIH have excluded liver injury associated with check point inhibitors as a phenotype of AIH.[35] Indeed, it would not have been possible to use the same criteria for liver injury caused by immune checkpoint inhibitors as the other drugs.

As patients who present with different acute and chronic liver diseases can have associated autoantibodies in serum, including patients with DILI,[12–18] it is obviously not sufficient for the diagnosis of DI-AILH to have a drug etiology and positive autoantibodies.

In the European Association for the Study of Liver (EASL) clinical guidelines for autoimmune hepatitis,[36] the authors stated that "of the several diagnostic challenges associated with this disease, the issue of drug-induced (like) AIH is the most complex and is not fully understood."[36]

Previous studies have not been able to distinguish DI-AILH from idiopathic AIH, clinically, biochemically, immunologically, or histologically.[5,9,26] In a study from the Mayo Clinic, the only feature that was found to distinguish these patients with DI-AILH from AIH was the lack of relapse after discontinuation of the IS in the former, whereas most of the other patients with AIH had a relapse of their AIH.[5] Similarly, in a large cohort of infliximab-induced DILI, relapse was not observed in those treated with corticosteroids.[7] Thus, the general rule of lack of relapse in patients treated with corticosteroids for DI-AILH was due to methyldopa, nitrofurantoin, hydralazine, minocycline, and infliximab. According to the clinical practice guidelines of AIH from the American Association for the Study of Liver Diseases and EASL, the DI-AILH clinical phenotype is considered to be associated with a lack of relapse, whereas when these patients experience a relapse they should be classified rather in the *idiopathic* AIH category.[35,36]

However, it is conceivable that drugs can trigger classic AIH. In the current study, this was almost exclusively associated with statins, which were the only type of drugs that fulfilled criteria 5 of being suspected of inducing chronic AIH.

The criteria used in the current study relied on positive autoimmune markers with a histology compatible with AIH, incomplete recovery or worsening of liver tests after stopping the implicated agent, need for corticosteroids to improve the liver injury, and lack of relapse after stopping corticosteroids. At least three of four indicated possible, whereas the first four criteria were needed to define probable DI-AILH. The current criteria have limitations. It is conceivable that some patients who do not improve in liver tests might respond to corticosteroids, although they lack autoantibodies. It was also difficult in some reports to assess whether there was incomplete recovery of liver tests after stopping the implicated agent. Furthermore, it was not always easy to dismiss IS due to the underlying condition. Only two cases of liver injury associated with minocycline with autoimmune features have been reported to relapse after discontinuation of corticosteroids.[37,38] Therefore, there have been exceptions in terms of minocycline, but to our knowledge relapse has not been reported after corticosteroid treatment of DI-AILH due to methyldopa, hydralazine, nitrofurantoin, and infliximab. There are rare exceptions to this general rule, however; it can be concluded based on the results of the current study that patients found to have well-documented DI-AILH due to drugs such as interferon, imatinib, diclofenac, and methylprednisolone would not require a long-term IS. All patients who had IS withdrawn after DI-AILH related to drugs that fulfilled the criteria for probable DI-AILH (except 1 patient with adalimumab with autoimmune features) did not relapse. Thus, there appears to be little doubt that a very high probability of these patients will stay in remission after corticosteroid treatment, in contrast to those with idiopathic AIH who mostly relapse without IS.[5,39] This is important in the historical perspective, as patients who developed DI-AILH due to interferon alpha and interferon beta, which was the most common type of drug found to induce DI-AILH, were not reported to have their IS discontinued in reports from 1989 to 2004. When this was first tried in 2006 and thereafter, it was always successful without relapse. Similarly, imatinib, a protein-tyrosine kinase inhibitor, was found to have several reports of convincing DI-AILH without a single case of relapse, suggesting that this type of drug does indeed induce DI-AILH, and not simply trigger classical AIH.

The proportion of females was high in drugs convincingly leading to DI-AILH in the current study (interferons [86%], imatinib [60%], adalimumab [90%], and methylprednisolone [94%]), which is in line with previous reports of DI-AILH.[5,6] We do not have an explanation for the induction of DI-AILH by high-dose methylprednisolone, and it also appears to be able to induce liver injury without autoimmune features.[40] We are not aware of other corticosteroids that can lead to DI-AILH.

Although a substantial number of cases of statin-induced DI-AILH was reported, only 4 of 24 (17%) probable DI-AILH cases were observed. There were a few convincing cases due to statins, and statins might be able to induce DI-AILH. Relapse was frequently observed in the statin reports, and it is conceivable that the statins might have triggered a classical AIH. Same was true for diclofenac: Three cases fulfilled the criteria of probable DI-AILH, but strangely enough all were from the early 1990s.

Although we were able to find a total of 38 reports of suspected HDS-induced DI-AILH, only two compounds were found to fulfill the criteria for probable DI-AILH. The use of khat and Tinospora cordifolia both had three probable DI-AILH cases reported. Interestingly, all except 1 patient (86%) using Tinospora cordifolia were female, whereas all khat (cathinone and cathine are the active ingredients, structurally related to amphetamine)

users were male, as chewing khat leaves is a common social tradition especially among men. Khat has been reported to have serious hepatic complications and has been associated with the development of liver cirrhosis.[41]

There were various reasons for lack of fulfillment of criteria for DI-AILH in terms of both conventional drugs and HDS. In many of the reports, patients with DILI were described who had positive autoantibodies that spontaneously disappeared after discontinuation of the implicated agent. Furthermore, in some cases with very short drug exposure, drugs might have been consumed for symptoms of previously unrecognized AIH, and in several cases probably innocent bystanders who presented with idiopathic AIH. However, it was reported from the Spanish Hepatotoxicity Registry that among patients with at least two episodes of DILI caused by different drugs, 4 of 9 (44%) presented with AIH in the second episode.[42]

The current study has some strengths. A relatively large number of reports were analyzed systematically based on predetermined criteria. The proposed criteria also create some limitations, as they have not been validated and there is no consensus in the literature on their use. The major drawback of the analysis was a heterogenous and inconsistent presentation of the cases, which made interpretation of data difficult. Human leukocyte antigen typing was only presented in a minority of cases. Many case reports failed to provide important data for causality assessment and data used in the NSC. The NSC have not been validated in acute presentation of AIH.[29] It can be argued that the current analysis could have been a subject of systematic review. However, case reports very rarely have adequate search terms, which does not allow for a systematic review, and cases were mostly found by scrutinization of reference lists of the various case reports. It is conceivable that some case reports might have been missed.

In conclusion, the criteria proposed in this study may help to distinguish the phenotype of DI-AILH from idiopathic AIH. Clinicians should strongly consider stopping corticosteroids in patients in biochemical remission from liver injury associated with drugs found to induce probable DI-AILH in the current study.

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CONFLICT OF INTEREST

Nothing to report.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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