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Nomenclature, Diagnosis and Management of Drug-induced Autoimmune-like hepatitis (DI-ALH): An expert opinion meeting report

--Manuscript Draft--

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Editor-in-Chief, *Journal of Hepatology*

Dear Paolo Angeli,

Please find enclosed the manuscript by Raul J Andrade et al., titled "Nomenclature, Diagnosis and Management of Drug-induced Autoimmune-like hepatitis (DI-ALH): An expert opinion meeting report". This meeting report paper was previously agreed on to be submitted to J Hepatology.

Neither the entire paper nor any part of its contents has been published or accepted elsewhere. We believe the paper may be of particular interest to the readers of the journal because this paper summarizes the major topics discussed at the joint International Conference held between the Drug and Herbal & Dietary Supplement-Induced Liver Injury (DHILI) consortium and the International Autoimmune Hepatitis Group (IAIHG9) held in March 2022 in Nerja, Spain; both endorsed by The European Association for the Study of the Liver (EASL). Additionally, in this article we include an assessment of currently used definitions, and management strategies, proposing research topics and future directions of DI-ALH.

Please, do not hesitate to contact us if there is any question concerning this manuscript.

Thank you and best regards

Raul Andrade and M Isabel Lucena,

on behalf of the co-authors

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AUTHORS' REPLY TO EDITOR & REVIEWERS

Title: Nomenclature, Diagnosis and Management of Drug-induced Autoimmune-like hepatitis (DI-ALH): An expert opinion meeting report

Authors: Raúl J. Andrade et al.

Journal: Journal of Hepatology

We are very thankful to the editors and reviewers for their thorough examination and thoughtful analysis of our manuscript. We have carefully considered all the suggestions made by the reviewers and incorporated them into the paper. We believe that by implementing the suggested changes that were within our capacity, we have substantially improved the manuscript. Please, note that two new authors, Miren García-Cortes and Edmond Atallah, have been included for their outstanding contribution to the new data added in the text. Additionaly, we have realized that the author Anna Licata was not included in the list. We apologize to the journal for this oversight. The change in author's list has been approved by all co-authors including the added authors. Additionally, as a result of the modifications incorporated in the text, some references have been added, eliminated or renumbered.

We sincerely hope that we have addressed all the reviewers' comments to their satisfaction. All changes made in the original manuscript are highlighted in red in the revised version. We are confident that our manuscript has been improved with your insightful comments. We hope that our revised manuscript will be acceptable for publication in Journal of Hepatology. Please find below the replies to the editors' and rewiers' comments.

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Point-by-Point Response to the Editors and Reviewer's Comments.

Editor comments:

Dear Dr Lucena, the Editors and two reviewers have thoroughly evaluated this paper. First, we thank you for submitting this report to the Journal. We tend to agree with the first reviewer that the overall impression is somehow underwhelming. It may simply due to the lack of data on DI-ALH but the report and the expert meeting does not provide much more than a careful literature review. it is very unfortunate that 2 hot topics are being excluded namely immune checkpoint inhibitors and the COVID19 vaccine (numerous reports are now available for the latter).

Response: Thank you for your comment. We realize that the expert opinion meeting did not come up with straightforward concepts and definitions of what DI-ALH is, which is a clear indication of existing gaps in the topic. However, we believe this conference provides consensuses on the nomenclature, classification, diagnosis and management of DI-ALH, and identifies the more urgent research needs. As mentioned in the original version of the manuscript, liver injury due to checkpoint inhibitors and vaccine-induced liver injury were not discussed at the consensus meeting. The former type of DILI is generally not associated with autoimmune features and, at the time of the meeting, only a few case reports had emerged with liver injury due to the COVID-19 vaccine. However, we agree that it is important to cover these two "hot topics" in the manuscript, thus, the text has been updated with additional information regarding these two entities (COVID-19 vaccine and immune checkpoint inhibitors) as suggested.

Conversely, some of the drugs responsible of DI-ALH are no longer commercialized and this is the case for minocycline in France, for instance, minocycline being the example chosen for Figure 1.

Response: We thank the editor for highlighting this issue. Minocycline is an FDA-approved drug that is used in many parts of the world, including India and China that together account for a third of the world's population. Minocycline is one of the prototype drugs that demonstrates the role of adaptive immunity in the pathogenesis of DILI with a strong association with HLA-B*35:02. (Urban TJ, et al. Minocycline hepatotoxicity: Clinical characterization and identification of HLA-B∗35:02 as a risk factor. J Hepatol. 2017;67(1):137-144.) This is similar to the example of halothane-induced DILI in illustrating the role of the hapten hypothesis. Unlike halothane, minocycline is widely used worldwide except for a few countries, like recently in France.
Moreover, herbal DILI is increasing worldwide. Indeed, many herbals have characteristic features of drug-induced autoimmune like hepatitis. For example, Nagral and colleagues showed features of DI-ALH in 4 of their six patients with Giloy (Tinospora cordifolia) induced DILI precipitating acute on chronic liver failure. (Nagral A et al. J Clin Exp Hepatol 2021;11:732–738). Therefore, a manuscript on DI-ALH is pertinent and timely.

We do understand that this report is based on a conference that was held in March 2022 however for the purpose of publication we suggest that the manuscript goes further than those particular

proceedings while taking advantage of the large group of expert co-authors involved. In that sense we encourage a resubmission if more precise recommendations can be issued (see reviewer #1) and if those 2 classes of drugs/vaccines mentioned above can be covered.

Response: As stated on the previous version of the manuscript (last paragraph, page 11), due to some substantial differences with AILH in their clinicopathological phenotypes, serum laboratory profiles and associated mechanisms of action, immune-related liver injuries caused by members of the biological class of immune checkpoint inhibitors were previously excluded from further consideration in the manuscript. However, we agree in covering this topic, thus we have included a section on immune checkpoint inhibitors in this revised version (page 15-16).

On the other hand, as COVID-19 vaccine induced liver injury was an emerging topic based on anecdotical reports prior to the conference, this was not one issue discussed at the meeting. However, we acknowledge that important original papers have been recently published on this topic and further evidence has been added on this topic in the revised version (page 16-17).

Reviewer #1:

The paper is structured as a narrative review and identifies 5 key points relevant for Drug-induced Autoimmune-like hepatitis. As such it is unclear to me what the added value of this conference has been. The paragraphs on pages 12-23 summarize the literature and while many of the participants have contributed to the literature, the conference was not needed for this.

Response: Thank you for your comment. We acknowledge that the expert opinion meeting did not provide clear concepts and definitions of what DI-ALH is, which is clearly due to existing gaps in the field. Nonetheless, we think the conference provides consensus on the nomenclature, classification, diagnosis and management of DI-ALH, and identified the more urgent research needs. Furthermore, adding data on herbal-induced liver injury with autoimmune features, as well as checkpoint inhibitor and vaccine-induced liver injury with signs of autoimmunity, as suggested by the reviewer, has made the report even stronger.

The meat of the paper comes at page 24 "Current gaps and future steps of research to improve the analysis and management of DI-ALH' which provides a laundry list of gaps on clinical diagnosis and management of Drug-induced Autoimmune-like hepatitis that participants agreed upon. Was this part of a delphi process? Could the authors tell us how this list has been established was the support for this list uniform?

Response: Thank you for raising these interesting points. There was not a formal Delphi process. Speakers were asked to provide a list of gaps in knowledge & research agenda on the various

topics they addressed, which were further discussed and agreed upon during the meeting and in the subsequent drafting of the manuscript.

The key points tell me that Drug-induced Autoimmune-like hepatitis 'may be indistinguishable from autoimmune hepatitis' but as a clinician 'distinguishing is crucial' but alas there is 'lack of specific markers' to make the distinction. I want to challenge this group of experts. Show me a minimum set of characteristics that should veer my attention towards the diagnosis. I realize that we need time to observe and add clinical datapoints to make the case, but the authors are uniquely positioned to help the field. While table 5 is helpful (I think that this is the major yield of the paper) it reads like a grocery list or a case record form for a registry. I understand that this is what I need, but what I do want to know how to interpret the data when I see the patient with a possible Drug-induced Autoimmune-like hepatitis. So, while I acknowledge that there is a large degree of uncertainty and the authors are very cautious in their statements I would have liked to see a manuscript that veered away from a narrative review and focuses on concepts / teaching points / algorithms that can help me as a hepatologist in clinical practice.

Response: The points are well taken. We agree with the reviewer that there is a large degree of uncertainty concerning the diagnosis and management of these patients which indeed motivated DILI and AIH experts to meet and agree on the definitions and controversial issues. At the current time, unfortunately, there are no distinguishing clinical, biochemical and histological features between the two entities whether we like it or not. What we think is of importance in clinical practice is to be aware that some drugs have well-documented ability to induce AIH-like phenotype and these patients might not need life-long immunosuppression, which sometimes has been the case. The point is well taken that algorithm is helpful and we have added an algorithm to illustrate the different clinical scenarios and appropriate management. Therefore, a new statement has been added on page 22, and a management algorithm is illustrated in Figure 3.

Reviewer #2:

This report derived from a recent expert opinion meeting details the diagnosis and Management of Drug-induced autoimmune-like hepatitis (DI-ALH). DI-ALH is the term appropriately recommended by the meeting participants. The subject is comprehensively reviewed, and identifies the many areas of uncertainty and needs for further research. My only comment is the discrepancy in the text and Key Points regarding the statement that "absence of relapse on long

term follow up without immunosuppressive therapy is an important feature of DI-ALH". Yet on page 22, line 56, it is stated that in "DI-ALH Cases in Two prospective registries the likelihood of relapse increased over time reaching 50% after 4 more than4 years of follow up" on the following page 23 line 2 , "but in a fraction of cases liver injury do progress to chronicity and a self -perpetuating autoimmune liver disease ensues". I would not regard 50% of cases relapsing after 4 years as a fraction, and it contradicts the Key point. The AASLD 2019 guidelines on AIH state that such cases of relapse suggests underlying AIH. Could the authors clarify their position as regards this apparent contradiction and whether the meeting felt such cases of relapse were indeed AIH?

Response: We are very thankful to the reviewer for giving us the opportunity to clarify this point. Analysis of the cases of suspected DI-ALH cases reported in the literature (reference 24) revealed that in the vast majority of cases reported with well-documented drugs, no relapse was reported. However, in unselected DILI patients with autoimmune features this might be different. This just illustrated the need for a close follow-up of these patients. If these represent a DI-ALH with a relapse or an underlying AIH is still an open question.

We have tried to address this issue in Figure 2. We had only one case of DI-ALH due to nitrofurantoin, who did have a spontaneous relapse after 4 years of follow-up. This case clearly underscores the need for a long-term follow-up in these patients. To make this clearer, we have removed the word “fraction” and replaced it by “in some”.

A minor point is that line 1&2 on page 16 could be omitted as it is repeating the same information regarding Nitrofurantoin, minocycline and statins given earlier in the paragraph.

Response: Following the reviewer’s suggestion, lines 1&2 on page 16 have been deleted.

Editorial Team

The manuscript would benefit if the authors could despite all the unknowns agree on some guidance for the clinicians on how to proceed (e.g. diagnostic criteria or export recommendations).

Response: Thank you for your suggestions, this point is well taken. It has been considered in the new version of the manuscript and an algorithm has been added. See new Figure 3.

Nomenclature, Diagnosis and Management of Drug-induced Autoimmune-like hepatitis (DI-ALH): An expert opinion meeting report

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Disclaimer: This article reflects the views of the authors and should not be construed to represent the US FDA's views or policies or that of other regulatory agencies.

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Abstract

Drug-induced liver injury (DILI) can mimic almost all other liver disorders. A phenotype increasingly ascribed to drugs is autoimmune-like hepatitis (ALH). This article summarizes the major topics discussed at a joint International Conference held between Drug-Induced Liver Injury consortium and the International Autoimmune Hepatitis Group. DI-ALH is a liver injury with laboratory and/or histological features that may be indistinguishable from those of autoimmune hepatitis (AIH). Previous studies have revealed that patients with DI-ALH and those with *idiopathic* AIH have very similar clinical, biochemical, immunological and histological features. Differentiating DI-ALH from AIH is important as patients with DI-ALH rarely require long-term immunosuppression and often resolve spontaneously after stopping the culprit drug whereas patients with AIH mostly need long-term immunosuppression. Therefore, revision of the diagnosis on long-term follow up may be necessary in some cases. More than 40 different drugs including nitrofurantoin, methyldopa, hydralazine, minocycline, infliximab, herbal and dietary supplements such as Khat and Tinospora cordifolia have been implicated in DI-ALH. Understanding of DI-ALH is limited by the lack of specific markers of the disease that could allow a precise diagnosis and similarly, there is no single feature which is diagnostic of AIH. A management algorithm is proposed. There is an urgent need to prospectively evaluate patients with DI-ALH systematically to enable definitive characterization of this condition.

Key points

- DI-ALH is considered a liver injury with laboratory and/or histological features that may be indistinguishable from those of autoimmune hepatitis.
- Understanding of DI-ALH is limited by the lack of specific markers and similarly, there are no specific pathognomonic findings or individual biomarkers that can be used to establish a diagnosis of idiopathic AIH.
- Distinguishing DI-ALH from AIH is crucial since patients with DI-ALH rarely require long-term immunosuppression and often resolve spontaneously after stopping the culprit drug.
- The absence of relapse on long term follow up without immunosuppressive therapy is an important feature of DI-ALH.
- Further evaluation is needed to evaluate the utility of new biomarkers in the diagnosis of DI-ALH and its definitive characterization.

Foreword

The European Cooperation in Science & Technology (COST Action CA17112), 'Prospective European Drug-Induced Liver Injury Network' was established in 2018; and during a joint meeting with the International AIH Group (IAIHG) at the International Liver Congress, the annual meeting of the European Association for the Study of the Liver (EASL), it was decided to hold an International Expert Conference on Drug-Induced Autoimmune Hepatitis. The goals were to harmonize case-definitions, revisit the approach to diagnosis, and debate the merit of interventions with immunosuppressive therapy in circumstances where a drug is suspected of causing immune-mediated liver injury resembling AIH. This article summarizes the major topics discussed at the Conference, in March 2022 in Nerja, close to Malaga, Spain. This meeting is expected to expand collaborations between experts in AIH and in DILI, and address the identified gaps in knowledge by proposing a high-quality research program. The EASL has endorsed both the DHILI (Drug and Herbal & Dietary Supplement-Induced Liver Injury) consortium and the IAIHG (International Autoimmune Hepatitis Group) as official EASL consortia. This consensus report is timely due to the growing use of biologicals in the treatment of immune mediated diseases.

Introduction

Drugs, herbals, and dietary supplements can cause a variety of acute and chronic liver injuries in susceptible subjects, resulting in a variety of phenotypes that mimic almost all liver disorders (1). One of the phenotypes increasingly ascribed to drugs is what is frequently referred to as "drug-induced autoimmune hepatitis" in the literature, and hitherto will be termed autoimmune-like hepatitis (ALH) in this article (2). ALH events are characterized by histological features highly overlapping with '*idiopathic*' (classical) autoimmune hepatitis (AIH) and often associated with the presence of serum liver autoantibodies and elevated immunoglobulin G (IgG) levels (3). Currently, there are no specific pathognomonic findings or individual biomarkers that can be used to establish a diagnosis of idiopathic AIH. Diagnosis of AIH is based on clinical, biochemical, serological and histological features. These are often overlapping with those identified in patients with drug-induced ALH (4-6). Whether a given case of acute liver injury with an autoimmune phenotype is the drug-induced unmasking of subclinical AIH or *de novo* drug-induced liver injury (DILI) accompanied by autoimmune features may be difficult to distinguish (Table 1) (7). It is notable that several drugs and vaccines -recently COVID-19 vaccines- have been identified as triggers for the onset of AIH (8).

In contrast to a recognized high potential for chronicity or recurrence of hepatitis in AIH that requires long-term immunosuppressive therapy, ALH often resolves or improves upon withdrawal of the offending drug. Nonetheless, some patients with ALH may develop acute liver failure (ALF) or clinically significant chronic injury for whom long-term clinical follow-up may be warranted. Currently, there are no predictive markers that identify such individuals. With high rates of lasting resolution of liver injury in most patients with ALH after drug discontinuation, optimal management and requirement of immunosuppressants for this condition have yet to be elucidated. Defining optimal treatment regimens, duration of treatment or dosage protocols to manage ALH remains

an unmet challenge. The clinical value in optimizing such practices might reduce risk of adverse effects from immunosuppressive medications and associated healthcare costs (9). The International AIH Group (IAIHG) has sought to improve methods for the diagnosis and management of AIH and AIH-related conditions (5). In a partnership with the Prospective European Drug-Induced Liver Injury Network (10) and the IAIHG convened a conference, to establish a consensus for standardized nomenclature surrounding drug-induced ALH, best practices in management and identify key gaps in the diagnostic and mechanistic biomarkers. This article provides an overview of the major topics that were discussed at the workshop, including an assessment of currently used terminologies, management strategies, and future directions for research.

Terminology, case definition and phenotypic presentation

AIH is considered to be due to loss of immunological tolerance in liver tissue resulting in immune-mediated damage of the hepatic parenchyma (6,11,12). In genetically predisposed individuals, environmental factors are believed to initiate the self-perpetuating disease such as infections, but a definitive trigger has not been identified (5,6,12).

Idiosyncratic DILI affects only susceptible individuals and is less related to the drug dose (13). Since *idiosyncratic* DILI can rarely manifest with clinical, biochemical, immunological, and histological features resembling the phenotype of AIH, the two entities must be distinguished. Four terms denoting that DILI phenotype have been used in the published literature: drug-induced autoimmune hepatitis (DI-AIH) (14-18), "immune-mediated DILI" (19), "drug-induced liver injury with autoimmune features" (20) and drug-induced autoimmune-like hepatitis (DI-ALH) (4,21).

Nomenclature and diagnostic criteria of DI-ALH lack specificity. There is compelling evidence that *idiosyncratic* DILI is typically an immune-mediated disorder. The term "immune-mediated DILI" is also associated with many drugs that are not associated with well recognized autoimmune features (19,22,23).

Because autoantibodies can be found in many other liver disorders, DILI with "autoimmune features" is a descriptive and non-specific term. For these reasons 'DI-ALH (4) was chosen by many experts as the preferred term to specifically connote this condition. DI-ALH is referred to in the literature, as liver injury with laboratory and/or histological evidence of autoimmunity, high IgG levels, positive antinuclear (ANA), anti-smooth muscle (ASMA) and anti-liver-kidney microsomal. The liver damage in DI-ALH usually manifests clinically within three months of drug exposure, but can appear after more prolonged latency (14,15,19,21,24). The majority of DI-ALH cases present with an acute hepatocellular injury pattern but rarely cholestatic pattern (21). Evidence of hypersensitivity features like eosinophilia, fever, or rash are usually absent (Table 2). DI-ALH has been well documented for minocycline, nitrofurantoin, hydralazine, methyldopa, interferon, imatinib, adalimumab and infliximab (21,24). After withdrawal of the causal drug, the liver injury resolves in the vast majority (14,21), either spontaneously within 6 months or with corticosteroids (14,21). The lack of a reliable diagnostic biomarker and evidence-based treatment paradigm has resulted in limited guidance on how to manage this aspect of DILI (2,5,6,25-27).

Epidemiology

Idiopathic AIH is characterized by a chronic progressive course resulting in fibrosis, liver failure and death if left untreated (28). A recent meta-analysis shows a pooled worldwide annual incidence and prevalence of AIH of 1.37 and 17.4 per 100.000 persons (29). In

prospective studies, the crude incidence of DILI was estimated to be 14-19 cases per 100,000 inhabitants annually, respectively (30,31). Among 261 AIH patients, 24 (9.2%) were diagnosed retrospectively as cases of DI-ALH (17). Among DILI cohorts, 3-8.8% can be classified as DI-ALH cases (18,24,32). In the Spanish DILI Registry 1.2% of patients had two DILI episodes caused by different drugs, and these patients were more likely to present with autoimmune features in the second episode (7).

Drugs linked to DI-ALH

More than 40 different agents have been implicated to induce ALH (3). Metabolites from dihydralazine and tienilic acid coupled with cellular proteins can form neoantigens (4) inducing immune reactions causing DI-ALH (18,33). A summary of drugs suspected to lead to DI-ALH is presented in Table 3. Previous studies comparing patients with DI-ALH to those with AIH found similar clinical, biochemical, immunological, and histological features, with the exception of cirrhosis being less common in the DI-ALH group, and no recurrence after discontinuation of immunosuppression (14). Several studies have observed the absence of relapse in DI-ALH patients (14,17,34,35) whereas the vast majority of AIH patients relapse after stopping immunosuppressive therapy (36). Minocycline, nitrofurantoin, methyldopa, and infliximab are the most commonly implicated culprits (4,14,24,32,37), alongside emerging reports of vaccine-induced immune hepatitis (8). Other reported causative agents of DI-ALH include interferon, statins, methylprednisolone, adalimumab, imatinib, diclofenac, tinospora cordifolia and Khat (21).

Checkpoint inhibitor-induced liver injury (ChILI)

Checkpoint inhibitor-induced liver injury (ChILI) is accounting for increasing proportion of recent DILI cohort studies (10,38). The pattern of injury is hepatocellular in around

60% of cases. Checkpoint inhibitor therapy-related cholangiopathy with progression to bile duct loss has also been reported (39).

In a retrospective study comparing serological profile of ChILI cases with AIH, 94% of ChILI cases had normal immunoglobulin G (IgG). ANA and SMA positivity was detected in both conditions, but was more common in AIH (84%) than in ChILI (32%) (40). Liver biopsy can improve diagnostic certainty as well as avoid unnecessary immunosuppression in a proportion of cases. In 11% of patients with suspected ChILI, histology suggested an alternative pathology such as malignancy or DILI due to another concomitant drug (41). ChILI shows less severe confluent necrosis and plasma cell infiltration, fewer CD4+ and more CD8+ infiltrating lymphocytes in liver biopsies than classical AIH (42). Consistent with the current practice, steroids were administered in 59% before the performing liver biopsy according to clinical guidelines but some patients improved without the need for immunosuppression (38,43).

Autoimmune like hepatitis after SARS-CoV-2 vaccination

Shortly after vaccination campaigns started, the first case of possible AIH related to SARS-CoV-2 vaccine was published (44). Several case reports and case series followed, and an autoimmune phenotype observed with all COVID-19 vaccines (45). Liver tests showed a hepatocellular pattern in the vast majority of cases (84%). Most were females (63%) and onset occurred a median of 15 days after vaccination (45). The liver injury was symptomatic in most patients, with a single patient evolving to acute liver failure requiring a liver transplantation. An immune phenotype as defined by positivity for autoantibodies and elevated IgG levels was detected in 57% of the cases. Overall, 75% tested positive for ANA, and polyreactive IgG with reactivity against BSA/HIP1R (a new biomarker for AIH with a reported higher specificity than conventional autoantibodies) was detected in almost the half of the patients (8). Histology showed lobular hepatitis

(76%), and portal hepatitis (17%) with fibrosis being more prominent in the latter, which favored the diagnosis of DI-ALH rather than AIH, despite the fact that simplified IAIHG scoring (46) indicated that 82% of the patients had typical or probable AIH and ERN histology system indicated that 92% of patients had likely or possible AIH (3). The majority of the patients received immunosuppression with steroids, and liver enzymes normalized in two-thirds after 6 months. The vast majority of cases did not experience a relapse of liver injury, although follow-up was not prolonged in many cases. This is consistent with a DI-ALH phenotype, rather than an unmasking of a genuine AIH. The temporal relationship between vaccination and the appearance of the liver injury, and the fact that hepatitis was diagnosed after the 2nd vaccine dose in the majority of cases (8) suggested causality. In contrast, relapse of liver injury after a new dose of vaccine occurred in only 25% of cases, which challenges the causal relationship or reflects adaptation to the vaccine (8).

Clinical phenotypes

A frequent challenge is to differentiate the clinical presentation of DILI from AIH, since there is no differentiating biomarker between the two entities (47). In a recent study (21), five criteria were proposed to define DI-ALH based on cases of suspected DI-ALH published in the literature. Histological characteristics do not seem to allow distinction between these entities (14,16,17). Whilst a greater degree of fibrosis has been reported in AIH (14,16,48), this may be a reflection of disease chronicity rather than reflective of aetiology.

Different case series of patients with DI-ALH describing the response to immunosuppressant therapy are presented in Table 2. Corticosteroid responsiveness was similar in both DI-ALH and the AIH groups (14). Discontinuation of immunosuppression

was successful in all DI-ALH cases, whereas 65% of the AIH patients had a relapse after immunosuppression withdrawal (14), as observed in other studies (34,35). No relapses were observed after short-term immunosuppression therapy in the studies by Rodrigues *et al.* (infliximab and adalimumab) (34) and by Björnsson *et al*. (infliximab) (49,50). Interestingly, in the recent analysis of DI-ALH of the Spanish and the Latin-American registries, the probability of a relapse in patients grouped as DI-ALH increased with time, being 17 % at 6 months and 50 % after 4 years of follow-up after remission (51). In a retrospective longitudinal cohort of patients with drug-induced jaundice (n=685), 3.4% (n=23) patients were hospitalized (during a mean follow up of 10 years) of which 22% (n=5) developed autoimmune hepatitis at 1.5months to 6 years from the initial event and another 5 developed cryptogenic cirrhosis (52). This highlights the challenges in distinguishing DI-ALH and AIH; equally as evidence for chronicity of DI-ALH and therefore the need for long-term follow-up.

Diagnosis

Differentiating DI-ALH from AIH is crucial since most studies published suggest that patients with DI-ALH often resolve spontaneously after stopping the culprit drug and rarely require long-term immunosuppression. Timing of the diagnosis is critical for the management of both DI-ALH and AIH. Failure or late diagnosis in both cases can result in poor clinical outcomes (24).

Auto-antibodies

ANA and other autoantibodies are frequently associated with DI-ALH. A limitation in using ANA and SMA is their variability among different populations since they are absent or have lower frequencies in some ethnicities (53). ANA and ASMA positivity is common

in the general population particularly in advancing age (54). Low level ANA and ASMA titers are present in 40-65% of patients with extra-hepatic autoimmunity, in the absence of liver disease (55). The presence of autoantibodies in DI-ALH is usually related to specific drug types such as methyldopa, hydralazine, minocycline, nitrofurantoin, statins and infliximab (19,56). Presence of auto-antibodies are frequent in DILI, regardless of the causative drug (57,58). Therefore, the occurrence of ANA might at least in some patients represent an epiphenomenon of the acute DILI episode, rather than constituting a specific disease entity of DILI phenotype. Table 4 shows the prevalence of these autoantibodies in healthy population compared with those in patients diagnosed with AIH. These also highlight the limitations of these markers in distinguishing DI-ALH from AIH.

Liver Biopsy

Liver biopsy has been recommended as one of the diagnostic tests when DI-ALH is suspected, if AIH remains a competing etiology (46,59) and if immunosuppressive therapy is contemplated (4,19). Liver biopsy is useful for confirmation of AIH-like histology and exclusion of other potential diagnoses (e.g., steatohepatitis). Histological features of AIH are infiltration with lymphocytes and plasma cells, interface hepatitis, rosette formation and emperipolesis (60). The specificity of emperipolesis and rosette formation for AIH has been questioned and might reflect disease severity rather than aetiology of liver injury (3). DI-ALH mimics the morphological pattern of AIH, including the prominent lympho-plasmocytic infiltrates in portal spaces and interface hepatitis (16). The parenchyma is also inflamed, and variable degrees of confluent necrosis (e.g., perivenular or panacinar necrosis) can occur. The spectrum of injury is variable and plasma cells are only increased in two thirds of the biopsies, and either an acute- or chronic-hepatitis pattern of injury can develop (Figure 1). A limited number of studies

comparing liver histology between DI-ALH and AIH have been undertaken (14,17,48). The microscopic findings that might help to discriminate those two conditions are largely unknown, except for advanced fibrosis (i.e., cirrhosis), which is observed only in AIH, but not DI-ALH (14,16,48). Thus, most of DI-ALH associated injury is clinically and histologically indistinguishable from AIH. Thus far, studies comparing DILI with AIH have included DILI cases more broadly and have not focused on comparison between AIH and DI-ALH (61).

DILI causality assessment methods

Among the causality assessment methods used for the diagnosis of DILI, Roussel Uclaf Causality Assessment Method (RUCAM) has previously been the most used in clinical research worldwide (62). Concerns have been raised on its poor reliability, validity and lack of clinical evidence from the domain criteria (63). Recently, a revised electronic version of RUCAM was developed, coined the Revised Electronic Causality Assessment Method (RECAM), using data from two large prospective DILI registries, the Drug-Induced Liver Injury Network (DILIN) and the Spanish DILI Registry (64). RECAM seems to lead to improved case identification, earlier diagnosis, and medical management of DILI cases (64). However, RECAM, like RUCAM, has so far not been designed to consider the specific emerging phenotypes like DI-ALH. The original IAIHG scoring system (59) was initially developed to define cohorts of AIH patients for clinical trials and in difficult cases; but new simplified version more in clinical practice (60). The use of the IAIHG scoring systems (57) in DI-ALH patients should be further evaluated and compared with the new simplified criteria (60).

New Biomarkers and approaches

The use of autoantibody profiling has been explored to investigate and develop diagnostic tests that may help distinguish between DI-ALH from AIH. Lammert et al., demonstrated

that AIH was characterized by a group of both IgG and IgM autoantibodies while DI-ALH was only characterized by IgM, which could be used as a feature to distinguish DI-ALH from AIH (63). Four IgM autoantibodies directed at dsDNA (SCL-70, ssDNA, U1-snRNP-BB) were able to differentiate DI-ALH from DILI (AUC, 0.87) (65). This study was limited by less than strict criteria for DI-ALH as well as drugs that were not definitively associated with DILI with autoimmune features. In another study by Taubert et al., protein microarrays were used to identify polyreactive immunoglobulins G (plgG) being elevated in AIH (66). According to the authors, plgG might be a new future marker in order to facilitate diagnosis that could help to preselect liver disease patients for biopsy, because of higher specificity and overall accuracy than routine autoantibodies (e.g. ANA, SMA, LKM) (66).

Management and treatment of DI-ALH

Information is scarce on the management of DI-ALH and comes mainly from retrospective studies. Treatment decisions are often based on experience gained from case reports or expert opinion (14,16,34,35,48,50,51). The most important initial step in terms of management of any suspected DILI is to discontinue the implicated agent. Delays in withdrawal of the suspected precipitant drug may impact both the severity of injury and responsiveness to therapy. Published DI-ALH cases reported high rates of spontaneous recovery after discontinuation. Resolution may not appear immediately and ongoing or even worsening liver injury can occur despite the withdrawal of the suspected culprit drug (24,50). The type of liver injury should be assessed because in the case of persistent hepatocellular or mixed type liver injury steroid therapy can be necessary (47).

A management algorithm is illustrated in Figure 3. EASL guidelines suggest that steroid treatment should be evaluated following a multidisciplinary approach, and based on the patient's clinical and histopathologic features (2). Patients with suspected DI-ALH should

undergo detailed evaluation including a liver biopsy in most cases. Concerning histology, the validation cohort of the new simplified criteria did not include DI-ALH patients (46). It is not clear if the results of histology, lack of improvement of liver tests after stopping the implicated drug or both should be used as the indication for corticosteroids in DI-ALH patients. An international collaborative study of all DILI cases retrieved from two prospective DILI registries using propensity score analysis found benefit from steroid therapy (increase in the normalization rate of liver biochemistry) was more evident in patients with severe DILI (nR-based Hy's law) and no resolution at ≤ 30 days (67).

Although corticosteroids are often used to treat DI-ALH (68), the decision to institute corticosteroid therapy should ideally be individualized (69). Corticosteroids should be used in symptomatic patients if there is no improvement or worsening in liver tests after stopping the implicated agent. A short course of corticosteroids (1-2 months) could be considered in cases of protracted or increasing abnormalities in aminotransferases (21). It is not clear how long the clinician should wait for improvement and the current time it is based on clinical judgment. Corticosteroids may also be considered when rapid improvement in liver tests is desired in order to substitute the offending agent with an alternative drug (50). Recovery time was reported to be longer for DI-ALH than for DILI (8-10 weeks vs 5-7 weeks $p<0.05$) (70). However, the response to immunosuppressive treatment was found to be significantly faster in DI-ALH patients than for AIH patients (2 months vs 16.8 months) (71). Faster response or decrease of serum ALT within one week after initiation of corticosteroid treatment was observed in DILI compared to AIH patients (72). There is very limited data on the dose of corticosteroids used to treat DI-ALH in the published literature (17,31,32,34,35). In a recent study of patients with DI-ALH associated with infliximab, the median dose of prednisolone was 30 mg and in patients with jaundice 40 mg were used (50). While different studies have reported

distinct protocols and doses of steroids in AIH, there are still some uncertainties about the optimal management of these patients. Different authors agree that further work is still required to determine the optimal steroid induction protocol in patients with severe AIH (73). In the case of DI-ALH, steroid dosage is usually implemented based on the principal investigator's personal experience (74).

Rechallenge (re-administration of a drug suspected to have caused DILI) is currently the strongest proof of causality in the adjudication process of suspected DILI. Drug rechallenge in DILI cases is however potentially dangerous (2,75) and associated with risk of death or requirement of liver transplant (2,15,76). Despite the known risks, positive rechallenge can be considered if the patient has shown important benefits from the drug and other options are not available (76). The definition of positive rechallenge is currently defined as alanine transaminase (ALT) levels >3-5 upper limits of normal (ULN) after re-administration of the suspect drug, in a patient with normal baseline ALT (75). Information about positive or negative rechallenges in DI-ALH is very limited and restricted to individual cases. Therefore, information on rechallenge is lacking in DI-ALH and additional data needed from controlled clinical trials, prospective registries, and large health care databases.

Natural history

After the withdrawal of the causative agent and with institution of immunosuppression, the outcome in DI-ALH is generally good in most cases, with a low risk of relapse or progression to chronic liver injury as reported in different studies with heterogeneous follow-up (Table 2) (14,17,34,35,50). Interestingly, however, in a long-term follow-up of DI-ALH cases collected in two prospective DILI registries the likelihood of relapse increased over time, reaching 50% after more than 4 years of follow-up (51). Thus, DI-AHL presents as a "self-limited" phenotype that resolves or becomes quiescent when the

drug is removed, but in some of the cases, liver injury do progress to chronicity and a "self-perpetuating" autoimmune liver disease ensues (Figure 2) (22,51,52).

Normalization of liver tests, either spontaneously or after the use of immunosuppression, in DILI patients did not always guarantee a benign course and highlights the need for prolonged follow up and/or AIH development after resolution of DILI (52,77). Additionally, early identification of patients with DI-ALH who would progress to ALF is still challenging (78). An algorithm developed by the Spanish DILI Registry to identify patients at higher risk of ALF at DILI recognition showed 82% specificity and 80% sensitivity (79). However, this has not been replicated and it is unknown if this algorithm applies to DI-ALH.

Implications for drug development

DILI is a major cause of the withdrawal of potentially valuable therapies post-marketing (80). Current methods have not been shown to be helpful in predicting DILI or DI-ALH in clinical studies (81). Due to the lack of effective biomarkers, Hy's law is currently the most commonly used tool available to the pharmaceutical industry for assessing a drug's potential to cause severe DILI. Therefore, the most specific indicator that a definite drug is hepatotoxic is the occurrence of drug-induced hepatocellular injury with jaundice, and/or an increased International Normalized Ratio (INR) (82). Labelling cases as potential DI-ALH in clinical trials may trigger follow-up actions, including: determining liver-specific autoantibodies in patients with elevated aminotransferases, administering steroids according to current recommendations for treatment of AIH, and long-term follow-up of study subjects to monitor for possible flares of AIH in either the presence or absence of study drug. For this reason, caution should be exerted in classifying a case of suspected DILI as DI-ALH, since this can have a profound impact on the workup of these patients, the decision to interrupt or discontinue treatment and the overall safety

assessment of the developmental compound. A comprehensive identification of potential DI-AILH cases in clinical studies would require a dedicated initiative, for instance in the frame of a public-private partnership that specifically addresses this question and allows partner companies to share samples and data.

A much better understanding of the mechanisms underlying DILI and DI-ALH is essential to design new improved predictive models (82). Thus, future research should focus on applying new technological advances and constructing a systematic biological approach to understand the mechanism and identify initial pathways. This will allow the identification of new treatment targets and other environmental and genetic factors that also have a profound impact on the risk of an individual patient developing overt liver disease. This would allow physicians to stratify their patients according to their environmental and genetic factors and to adopt a personalized medicine approach for the treatment of DI-ALH.

Current gaps and future steps of research to improve the analysis and management of DI-ALH

Several gaps were identified in terms of clinical diagnosis and management which benefit future research on the mechanisms of prevention and treatment of DI-ALH. The participants reached a consensus regarding existing gaps in the field motivating more research.

- To define the precise epidemiology of DI-ALH, a correct diagnosis of the (auto)immune phenotype of DILI is necessary. Comprehensive identification of potential DI-ALH cases in clinical studies would require a dedicated initiative, preferably prospective studies that specifically addresses this question and allows partner companies to share samples and data.

- The use of a consensus definition of DI-ALH will allow analyses of larger populations based on the same criteria, to define the different classes of drugs/agents that can cause DI-ALH as an entity, for better understanding of the outcome and management of patients.
- There is lack of data and specific biomarkers to characterise and discriminate DILI vs AIH vs DI-ALH. It is imperative to improve liver histology evaluation to better characterize the patterns of DI-ALH. The experts agree on the need to develop a tool for diagnosing DI-ALH before the initiation of therapy.
- A systematic investigation of the type and pattern of autoantibodies detected in DI-ALH, adhering to dedicated methodological guidelines, with comparison to AIH is warranted to investigate whether they can serve as specific biomarkers for diagnosis, prognosis and response to treatment.
- The experts agree that information on the morphologic evaluation of liver biopsy can be augmented by using immunohistochemical and molecular techniques. Future studies incorporating immune cell phenotyping may help identify immunohistochemical markers useful for the diagnosis of DI-ALH. A properly designed biopsy study and the discovery of new molecular markers that can explore these options may provide clarity in the differentiation of DI-ALH and AIH.
- Testing for carriage of particular HLA alleles in selected cases will assist in the diagnosis of DILI or AIH. Further studies are needed to clarify AIH and DI-ALH genetic heterogeneity and pathogenesis. Moreover, there is a clear need for evaluating the use and effectiveness of genetic tests in the diagnosis and decision-making in the clinical context of AIH vs DI-ALH.
- The current identified gaps in the management of DI-AILH are: 1) which patients require immunosuppression, 2) standardization in treatment regimens such as dose

and duration of therapy in the event immunosuppression is administered and 3) when to withdraw therapy. Thus, a set of criteria for DI-ALH assessment including tests and follow-up that should be done in prospective studies has been recommended in the workshop (Table 5).

- A prospective assessment of predictors of positive rechallenge with the same or with a different drug and outcomes should be performed.
- Liver biopsies and conducting spatial profiling of gene signatures between DI-ALH and AIH would highlight the difference for future fine-tuning of nomenclature. Future research involving comparative analysis using distinct "omics" technologies may allow for categorizing DI-ALH cases to better predict their progression, spontaneous resolution, response to therapy and outcomes.
- The experts agreed that larger prospective studies with relevant follow-up information on immunosuppression are needed to properly characterize the natural history of DI-ALH. Moreover, since the progression of DI-ALH to ALF is uncommon, and there are no biomarkers predictive of disease progression, the experts recommend that patients with acute severe presentation should be referred and managed in centres with advanced hepatology care.

DI-ALH Management: Developing Guidelines

The lack of a reliable diagnostic biomarkers and evidence-based treatment paradigm has resulted in limited guidance on how to manage this aspect of DILI (2,25-27). DI-ALH was defined in the EASL Clinical Practice guideline (CPG) as "acute DILI with serological and/or histological markers of *idiopathic* AIH" (2).

Conclusions

In summary, DI-ALH as a clinical phenotype is poorly characterized. Establishing new collaborative initiatives will allow for a better understanding of the various DILI signatures. The term DI-ALH was preferred by the majority of experts to describe this clinical and biochemical phenotype. Closing this gap should be the primary focus of future collaborative research to advance this field, with the ultimate goal of developing novel targeted risk management and therapeutic strategies to optimally manage DILI, AIH and DI-ALH, using precision medicine approaches.

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"Author names in bold designate shared co-first authorship"

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LEGEND TO FIGURES

Figure 1. Liver biopsy findings in DI-ALH. (A) A biopsy of minocycline-related DI-ALH shows a chronic hepatitis pattern of injury with predominantly portal based inflammation and periportal fibrosis. Interface hepatitis is noted (arrows). (B) Higher magnification shows plasma cells aggregated at the interface. (C) A biopsy of nitrofurantoin-related DI-ALH demonstrates an acute hepatitis pattern of injury with predominantly lobular inflammation and perivenular confluent necrosis (arrow). (D) High magnification shows enlarged hepatocytes with cytoplasmic vacuolation, multinucleation and emperipolesis, against the background of lymphoplasmacytic infiltration.

Figure 2. Overlap between Drug-Induced liver injury (DILI), Drug-induced autoimmune-like hepatitis (DI-ALH) and idiopathic Autoimmune hepatitis (AIH). Limited number of DI-ALH patients progress into chronicity and evolve disease phenotype to more of an idiopathic AIH type.

Figure 3. An algorithm to approach suspected DI-ALH in clinical practice.

***Alternatively, in mild cases associated with specific drugs known to induce this phenotype (i.e. infliximab) with clinical/biochemical improvement a liver biopsy would not always be necessary

Nomenclature, Diagnosis and Management of Drug-induced Autoimmune-like hepatitis (DI-ALH): An expert opinion meeting report

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Abstract

Drug-induced liver injury (DILI) can mimic almost all other liver disorders. A phenotype increasingly ascribed to drugs is autoimmune-like hepatitis (ALH). This article summarizes the major topics discussed at a joint International Conference held between Drug-Induced Liver Injury consortium and the International Autoimmune Hepatitis Group. DI-ALH is a liver injury with laboratory and/or histological features that may be indistinguishable from those of autoimmune hepatitis (AIH). Previous studies have revealed that patients with DI-ALH and those with *idiopathic* AIH have very similar clinical, biochemical, immunological and histological features. Differentiating DI-ALH from AIH is important as patients with DI-ALH rarely require long-term immunosuppression and often resolve spontaneously after stopping the culprit drug whereas patients with AIH mostly need long-term immunosuppression. Therefore, revision of the diagnosis on long-term follow up may be necessary in some cases. More than 40 different drugs including nitrofurantoin, methyldopa, hydralazine, minocycline, infliximab, herbal and dietary supplements such as Khat and Tinospora cordifolia have been implicated in DI-ALH. Understanding of DI-ALH is limited by the lack of specific markers of the disease that could allow a precise diagnosis and similarly, there is no single feature which is diagnostic of AIH. A management algorithm is proposed. There is an urgent need to prospectively evaluate patients with DI-ALH systematically to enable definitive characterization of this condition.

Key points

- DI-ALH is considered a liver injury with laboratory and/or histological features that may be indistinguishable from those of autoimmune hepatitis.
- Understanding of DI-ALH is limited by the lack of specific markers and similarly, there are no specific pathognomonic findings or individual biomarkers that can be used to establish a diagnosis of idiopathic AIH.
- Distinguishing DI-ALH from AIH is crucial since patients with DI-ALH rarely require long-term immunosuppression and often resolve spontaneously after stopping the culprit drug.
- The absence of relapse on long term follow up without immunosuppressive therapy is an important feature of DI-ALH.
- Further evaluation is needed to evaluate the utility of new biomarkers in the diagnosis of DI-ALH and its definitive characterization.

Foreword

The European Cooperation in Science & Technology (COST Action CA17112), 'Prospective European Drug-Induced Liver Injury Network' was established in 2018; and during a joint meeting with the International AIH Group (IAIHG) at the International Liver Congress, the annual meeting of the European Association for the Study of the Liver (EASL), it was decided to hold an International Expert Conference on Drug-Induced Autoimmune Hepatitis. The goals were to harmonize case-definitions, revisit the approach to diagnosis, and debate the merit of interventions with immunosuppressive therapy in circumstances where a drug is suspected of causing immune-mediated liver injury resembling AIH. This article summarizes the major topics discussed at the Conference, in March 2022 in Nerja, close to Malaga, Spain. This meeting is expected to expand collaborations between experts in AIH and in DILI, and address the identified gaps in knowledge by proposing a high-quality research program. The EASL has endorsed both the DHILI (Drug and Herbal & Dietary Supplement-Induced Liver Injury) consortium and the IAIHG (International Autoimmune Hepatitis Group) as official EASL consortia. This consensus report is timely due to the growing use of biologicals in the treatment of immune mediated diseases.

Introduction

Drugs, herbals, and dietary supplements can cause a variety of acute and chronic liver injuries in susceptible subjects, resulting in a variety of phenotypes that mimic almost all liver disorders (1). One of the phenotypes increasingly ascribed to drugs is what is frequently referred to as "drug-induced autoimmune hepatitis" in the literature, and hitherto will be termed autoimmune-like hepatitis (ALH) in this article (2). ALH events are characterized by histological features highly overlapping with '*idiopathic*' (classical) autoimmune hepatitis (AIH) and often associated with the presence of serum liver autoantibodies and elevated immunoglobulin G (IgG) levels (3). Currently, there are no specific pathognomonic findings or individual biomarkers that can be used to establish a diagnosis of idiopathic AIH. Diagnosis of AIH is based on clinical, biochemical, serological and histological features. These are often overlapping with those identified in patients with drug-induced ALH (4-6). Whether a given case of acute liver injury with an autoimmune phenotype is the drug-induced unmasking of subclinical AIH or *de novo* drug-induced liver injury (DILI) accompanied by autoimmune features may be difficult to distinguish (Table 1) (7). It is notable that several drugs and vaccines -recently COVID-19 vaccines- have been identified as triggers for the onset of AIH (8).

In contrast to a recognized high potential for chronicity or recurrence of hepatitis in AIH that requires long-term immunosuppressive therapy, ALH often resolves or improves upon withdrawal of the offending drug. Nonetheless, some patients with ALH may develop acute liver failure (ALF) or clinically significant chronic injury for whom long-term clinical follow-up may be warranted. Currently, there are no predictive markers that identify such individuals. With high rates of lasting resolution of liver injury in most patients with ALH after drug discontinuation, optimal management and requirement of immunosuppressants for this condition have yet to be elucidated. Defining optimal treatment regimens, duration of treatment or dosage protocols to manage ALH remains

an unmet challenge. The clinical value in optimizing such practices might reduce risk of adverse effects from immunosuppressive medications and associated healthcare costs (9). The International AIH Group (IAIHG) has sought to improve methods for the diagnosis and management of AIH and AIH-related conditions (5). In a partnership with the Prospective European Drug-Induced Liver Injury Network (10) and the IAIHG convened a conference, to establish a consensus for standardized nomenclature surrounding drug-induced ALH, best practices in management and identify key gaps in the diagnostic and mechanistic biomarkers. This article provides an overview of the major topics that were discussed at the workshop, including an assessment of currently used terminologies, management strategies, and future directions for research.

Terminology, case definition and phenotypic presentation

AIH is considered to be due to loss of immunological tolerance in liver tissue resulting in immune-mediated damage of the hepatic parenchyma (6,11,12). In genetically predisposed individuals, environmental factors are believed to initiate the self-perpetuating disease such as infections, but a definitive trigger has not been identified (5,6,12).

Idiosyncratic DILI affects only susceptible individuals and is less related to the drug dose (13). Since *idiosyncratic* DILI can rarely manifest with clinical, biochemical, immunological, and histological features resembling the phenotype of AIH, the two entities must be distinguished. Four terms denoting that DILI phenotype have been used in the published literature: drug-induced autoimmune hepatitis (DI-AIH) (14-18), "immune-mediated DILI" (19), "drug-induced liver injury with autoimmune features" (20) and drug-induced autoimmune-like hepatitis (DI-ALH) (4,21).

Nomenclature and diagnostic criteria of DI-ALH lack specificity. There is compelling evidence that *idiosyncratic* DILI is typically an immune-mediated disorder. The term "immune-mediated DILI" is also associated with many drugs that are not associated with well recognized autoimmune features (19,22,23).

Because autoantibodies can be found in many other liver disorders, DILI with "autoimmune features" is a descriptive and non-specific term. For these reasons 'DI-ALH (4) was chosen by many experts as the preferred term to specifically connote this condition. DI-ALH is referred to in the literature, as liver injury with laboratory and/or histological evidence of autoimmunity, high IgG levels, positive antinuclear (ANA), anti-smooth muscle (ASMA) and anti-liver-kidney microsomal. The liver damage in DI-ALH usually manifests clinically within three months of drug exposure, but can appear after more prolonged latency (14,15,19,21,24). The majority of DI-ALH cases present with an acute hepatocellular injury pattern but rarely cholestatic pattern (21). Evidence of hypersensitivity features like eosinophilia, fever, or rash are usually absent (Table 2). DI-ALH has been well documented for minocycline, nitrofurantoin, hydralazine, methyldopa, interferon, imatinib, adalimumab and infliximab (21,24). After withdrawal of the causal drug, the liver injury resolves in the vast majority (14,21), either spontaneously within 6 months or with corticosteroids (14,21). The lack of a reliable diagnostic biomarker and evidence-based treatment paradigm has resulted in limited guidance on how to manage this aspect of DILI (2,5,6,25-27).

Epidemiology

Idiopathic AIH is characterized by a chronic progressive course resulting in fibrosis, liver failure and death if left untreated (28). A recent meta-analysis shows a pooled worldwide annual incidence and prevalence of AIH of 1.37 and 17.4 per 100.000 persons (29). In

prospective studies, the crude incidence of DILI was estimated to be 14-19 cases per 100,000 inhabitants annually, respectively (30,31). Among 261 AIH patients, 24 (9.2%) were diagnosed retrospectively as cases of DI-ALH (17). Among DILI cohorts, 3-8.8% can be classified as DI-ALH cases (18,24,32). In the Spanish DILI Registry 1.2% of patients had two DILI episodes caused by different drugs, and these patients were more likely to present with autoimmune features in the second episode (7).

Drugs linked to DI-ALH

More than 40 different agents have been implicated to induce ALH (3). Metabolites from dihydralazine and tienilic acid coupled with cellular proteins can form neoantigens (4) inducing immune reactions causing DI-ALH (18,33). A summary of drugs suspected to lead to DI-ALH is presented in Table 3. Previous studies comparing patients with DI-ALH to those with AIH found similar clinical, biochemical, immunological, and histological features, with the exception of cirrhosis being less common in the DI-ALH group, and no recurrence after discontinuation of immunosuppression (14). Several studies have observed the absence of relapse in DI-ALH patients (14,17,34,35) whereas the vast majority of AIH patients relapse after stopping immunosuppressive therapy (36). Minocycline, nitrofurantoin, methyldopa, and infliximab are the most commonly implicated culprits (4,14,24,32,37), alongside emerging reports of vaccine-induced immune hepatitis (8). Other reported causative agents of DI-ALH include interferon, statins, methylprednisolone, adalimumab, imatinib, diclofenac, tinospora cordifolia and Khat (21).

Checkpoint inhibitor-induced liver injury (ChILI)

Checkpoint inhibitor-induced liver injury (ChILI) is accounting for increasing proportion of recent DILI cohort studies (10,38). The pattern of injury is hepatocellular in around

60% of cases. Checkpoint inhibitor therapy-related cholangiopathy with progression to bile duct loss has also been reported (39).

In a retrospective study comparing serological profile of ChILI cases with AIH, 94% of ChILI cases had normal immunoglobulin G (IgG). ANA and SMA positivity was detected in both conditions, but was more common in AIH (84%) than in ChILI (32%) (40). Liver biopsy can improve diagnostic certainty as well as avoid unnecessary immunosuppression in a proportion of cases. In 11% of patients with suspected ChILI, histology suggested an alternative pathology such as malignancy or DILI due to another concomitant drug (41). ChILI shows less severe confluent necrosis and plasma cell infiltration, fewer CD4+ and more CD8+ infiltrating lymphocytes in liver biopsies than classical AIH (42). Consistent with the current practice, steroids were administered in 59% before the performing liver biopsy according to clinical guidelines but some patients improved without the need for immunosuppression (38,43).

Autoimmune like hepatitis after SARS-CoV-2 vaccination

Shortly after vaccination campaigns started, the first case of possible AIH related to SARS-CoV-2 vaccine was published (44). Several case reports and case series followed, and an autoimmune phenotype observed with all COVID-19 vaccines (45). Liver tests showed a hepatocellular pattern in the vast majority of cases (84%). Most were females (63%) and onset occurred a median of 15 days after vaccination (45). The liver injury was symptomatic in most patients, with a single patient evolving to acute liver failure requiring a liver transplantation. An immune phenotype as defined by positivity for autoantibodies and elevated IgG levels was detected in 57% of the cases. Overall, 75% tested positive for ANA, and polyreactive IgG with reactivity against BSA/HIP1R (a new biomarker for AIH with a reported higher specificity than conventional autoantibodies) was detected in almost the half of the patients (8). Histology showed lobular hepatitis

(76%), and portal hepatitis (17%) with fibrosis being more prominent in the latter, which favored the diagnosis of DI-ALH rather than AIH, despite the fact that simplified IAIHG scoring (46) indicated that 82% of the patients had typical or probable AIH and ERN histology system indicated that 92% of patients had likely or possible AIH (3). The majority of the patients received immunosuppression with steroids, and liver enzymes normalized in two-thirds after 6 months. The vast majority of cases did not experience a relapse of liver injury, although follow-up was not prolonged in many cases. This is consistent with a DI-ALH phenotype, rather than an unmasking of a genuine AIH. The temporal relationship between vaccination and the appearance of the liver injury, and the fact that hepatitis was diagnosed after the 2nd vaccine dose in the majority of cases (8) suggested causality. In contrast, relapse of liver injury after a new dose of vaccine occurred in only 25% of cases, which challenges the causal relationship or reflects adaptation to the vaccine (8).

Clinical phenotypes

A frequent challenge is to differentiate the clinical presentation of DILI from AIH, since there is no differentiating biomarker between the two entities (47). In a recent study (21), five criteria were proposed to define DI-ALH based on cases of suspected DI-ALH published in the literature. Histological characteristics do not seem to allow distinction between these entities (14,16,17). Whilst a greater degree of fibrosis has been reported in AIH (14,16,48), this may be a reflection of disease chronicity rather than reflective of aetiology.

Different case series of patients with DI-ALH describing the response to immunosuppressant therapy are presented in Table 2. Corticosteroid responsiveness was similar in both DI-ALH and the AIH groups (14). Discontinuation of immunosuppression

was successful in all DI-ALH cases, whereas 65% of the AIH patients had a relapse after immunosuppression withdrawal (14), as observed in other studies (34,35). No relapses were observed after short-term immunosuppression therapy in the studies by Rodrigues *et al.* (infliximab and adalimumab) (34) and by Björnsson *et al*. (infliximab) (49,50). Interestingly, in the recent analysis of DI-ALH of the Spanish and the Latin-American registries, the probability of a relapse in patients grouped as DI-ALH increased with time, being 17 % at 6 months and 50 % after 4 years of follow-up after remission (51). In a retrospective longitudinal cohort of patients with drug-induced jaundice (n=685), 3.4% (n=23) patients were hospitalized (during a mean follow up of 10 years) of which 22% (n=5) developed autoimmune hepatitis at 1.5months to 6 years from the initial event and another 5 developed cryptogenic cirrhosis (52). This highlights the challenges in distinguishing DI-ALH and AIH; equally as evidence for chronicity of DI-ALH and therefore the need for long-term follow-up.

Diagnosis

Differentiating DI-ALH from AIH is crucial since most studies published suggest that patients with DI-ALH often resolve spontaneously after stopping the culprit drug and rarely require long-term immunosuppression. Timing of the diagnosis is critical for the management of both DI-ALH and AIH. Failure or late diagnosis in both cases can result in poor clinical outcomes (24).

Auto-antibodies

ANA and other autoantibodies are frequently associated with DI-ALH. A limitation in using ANA and SMA is their variability among different populations since they are absent or have lower frequencies in some ethnicities (53). ANA and ASMA positivity is common

in the general population particularly in advancing age (54). Low level ANA and ASMA titers are present in 40-65% of patients with extra-hepatic autoimmunity, in the absence of liver disease (55). The presence of autoantibodies in DI-ALH is usually related to specific drug types such as methyldopa, hydralazine, minocycline, nitrofurantoin, statins and infliximab (19,56). Presence of auto-antibodies are frequent in DILI, regardless of the causative drug (57,58). Therefore, the occurrence of ANA might at least in some patients represent an epiphenomenon of the acute DILI episode, rather than constituting a specific disease entity of DILI phenotype. Table 4 shows the prevalence of these autoantibodies in healthy population compared with those in patients diagnosed with AIH. These also highlight the limitations of these markers in distinguishing DI-ALH from AIH.

Liver Biopsy

Liver biopsy has been recommended as one of the diagnostic tests when DI-ALH is suspected, if AIH remains a competing etiology (46,59) and if immunosuppressive therapy is contemplated (4,19). Liver biopsy is useful for confirmation of AIH-like histology and exclusion of other potential diagnoses (e.g., steatohepatitis). Histological features of AIH are infiltration with lymphocytes and plasma cells, interface hepatitis, rosette formation and emperipolesis (60). The specificity of emperipolesis and rosette formation for AIH has been questioned and might reflect disease severity rather than aetiology of liver injury (3). DI-ALH mimics the morphological pattern of AIH, including the prominent lympho-plasmocytic infiltrates in portal spaces and interface hepatitis (16). The parenchyma is also inflamed, and variable degrees of confluent necrosis (e.g., perivenular or panacinar necrosis) can occur. The spectrum of injury is variable and plasma cells are only increased in two thirds of the biopsies, and either an acute- or chronic-hepatitis pattern of injury can develop (Figure 1). A limited number of studies

comparing liver histology between DI-ALH and AIH have been undertaken (14,17,48). The microscopic findings that might help to discriminate those two conditions are largely unknown, except for advanced fibrosis (i.e., cirrhosis), which is observed only in AIH, but not DI-ALH (14,16,48). Thus, most of DI-ALH associated injury is clinically and histologically indistinguishable from AIH. Thus far, studies comparing DILI with AIH have included DILI cases more broadly and have not focused on comparison between AIH and DI-ALH (61).

DILI causality assessment methods

Among the causality assessment methods used for the diagnosis of DILI, Roussel Uclaf Causality Assessment Method (RUCAM) has previously been the most used in clinical research worldwide (62). Concerns have been raised on its poor reliability, validity and lack of clinical evidence from the domain criteria (63). Recently, a revised electronic version of RUCAM was developed, coined the Revised Electronic Causality Assessment Method (RECAM), using data from two large prospective DILI registries, the Drug-Induced Liver Injury Network (DILIN) and the Spanish DILI Registry (64). RECAM seems to lead to improved case identification, earlier diagnosis, and medical management of DILI cases (64). However, RECAM, like RUCAM, has so far not been designed to consider the specific emerging phenotypes like DI-ALH. The original IAIHG scoring system (59) was initially developed to define cohorts of AIH patients for clinical trials and in difficult cases; but new simplified version more in clinical practice (60). The use of the IAIHG scoring systems (57) in DI-ALH patients should be further evaluated and compared with the new simplified criteria (60).

New Biomarkers and approaches

The use of autoantibody profiling has been explored to investigate and develop diagnostic tests that may help distinguish between DI-ALH from AIH. Lammert et al., demonstrated

that AIH was characterized by a group of both IgG and IgM autoantibodies while DI-ALH was only characterized by IgM, which could be used as a feature to distinguish DI-ALH from AIH (63). Four IgM autoantibodies directed at dsDNA (SCL-70, ssDNA, U1-snRNP-BB) were able to differentiate DI-ALH from DILI (AUC, 0.87) (65). This study was limited by less than strict criteria for DI-ALH as well as drugs that were not definitively associated with DILI with autoimmune features. In another study by Taubert et al., protein microarrays were used to identify polyreactive immunoglobulins G (plgG) being elevated in AIH (66). According to the authors, plgG might be a new future marker in order to facilitate diagnosis that could help to preselect liver disease patients for biopsy, because of higher specificity and overall accuracy than routine autoantibodies (e.g. ANA, SMA, LKM) (66).

Management and treatment of DI-ALH

Information is scarce on the management of DI-ALH and comes mainly from retrospective studies. Treatment decisions are often based on experience gained from case reports or expert opinion (14,16,34,35,48,50,51). The most important initial step in terms of management of any suspected DILI is to discontinue the implicated agent. Delays in withdrawal of the suspected precipitant drug may impact both the severity of injury and responsiveness to therapy. Published DI-ALH cases reported high rates of spontaneous recovery after discontinuation. Resolution may not appear immediately and ongoing or even worsening liver injury can occur despite the withdrawal of the suspected culprit drug (24,50). The type of liver injury should be assessed because in the case of persistent hepatocellular or mixed type liver injury steroid therapy can be necessary (47).

A management algorithm is illustrated in Figure 3. EASL guidelines suggest that steroid treatment should be evaluated following a multidisciplinary approach, and based on the patient's clinical and histopathologic features (2). Patients with suspected DI-ALH should

undergo detailed evaluation including a liver biopsy in most cases. Concerning histology, the validation cohort of the new simplified criteria did not include DI-ALH patients (46). It is not clear if the results of histology, lack of improvement of liver tests after stopping the implicated drug or both should be used as the indication for corticosteroids in DI-ALH patients. An international collaborative study of all DILI cases retrieved from two prospective DILI registries using propensity score analysis found benefit from steroid therapy (increase in the normalization rate of liver biochemistry) was more evident in patients with severe DILI (nR-based Hy's law) and no resolution at ≤ 30 days (67).

Although corticosteroids are often used to treat DI-ALH (68), the decision to institute corticosteroid therapy should ideally be individualized (69). Corticosteroids should be used in symptomatic patients if there is no improvement or worsening in liver tests after stopping the implicated agent. A short course of corticosteroids (1-2 months) could be considered in cases of protracted or increasing abnormalities in aminotransferases (21). It is not clear how long the clinician should wait for improvement and the current time it is based on clinical judgment. Corticosteroids may also be considered when rapid improvement in liver tests is desired in order to substitute the offending agent with an alternative drug (50). Recovery time was reported to be longer for DI-ALH than for DILI (8-10 weeks vs 5-7 weeks $p<0.05$) (70). However, the response to immunosuppressive treatment was found to be significantly faster in DI-ALH patients than for AIH patients (2 months vs 16.8 months) (71). Faster response or decrease of serum ALT within one week after initiation of corticosteroid treatment was observed in DILI compared to AIH patients (72). There is very limited data on the dose of corticosteroids used to treat DI-ALH in the published literature (17,31,32,34,35). In a recent study of patients with DI-ALH associated with infliximab, the median dose of prednisolone was 30 mg and in patients with jaundice 40 mg were used (50). While different studies have reported

distinct protocols and doses of steroids in AIH, there are still some uncertainties about the optimal management of these patients. Different authors agree that further work is still required to determine the optimal steroid induction protocol in patients with severe AIH (73). In the case of DI-ALH, steroid dosage is usually implemented based on the principal investigator's personal experience (74).

Rechallenge (re-administration of a drug suspected to have caused DILI) is currently the strongest proof of causality in the adjudication process of suspected DILI. Drug rechallenge in DILI cases is however potentially dangerous (2,75) and associated with risk of death or requirement of liver transplant (2,15,76). Despite the known risks, positive rechallenge can be considered if the patient has shown important benefits from the drug and other options are not available (76). The definition of positive rechallenge is currently defined as alanine transaminase (ALT) levels >3-5 upper limits of normal (ULN) after re-administration of the suspect drug, in a patient with normal baseline ALT (75). Information about positive or negative rechallenges in DI-ALH is very limited and restricted to individual cases. Therefore, information on rechallenge is lacking in DI-ALH and additional data needed from controlled clinical trials, prospective registries, and large health care databases.

Natural history

After the withdrawal of the causative agent and with institution of immunosuppression, the outcome in DI-ALH is generally good in most cases, with a low risk of relapse or progression to chronic liver injury as reported in different studies with heterogeneous follow-up (Table 2) (14,17,34,35,50). Interestingly, however, in a long-term follow-up of DI-ALH cases collected in two prospective DILI registries the likelihood of relapse increased over time, reaching 50% after more than 4 years of follow-up (51). Thus, DI-AHL presents as a "self-limited" phenotype that resolves or becomes quiescent when the

drug is removed, but in some of the cases, liver injury do progress to chronicity and a "self-perpetuating" autoimmune liver disease ensues (Figure 2) (22,51,52).

Normalization of liver tests, either spontaneously or after the use of immunosuppression, in DILI patients did not always guarantee a benign course and highlights the need for prolonged follow up and/or AIH development after resolution of DILI (52,77). Additionally, early identification of patients with DI-ALH who would progress to ALF is still challenging (78). An algorithm developed by the Spanish DILI Registry to identify patients at higher risk of ALF at DILI recognition showed 82% specificity and 80% sensitivity (79). However, this has not been replicated and it is unknown if this algorithm applies to DI-ALH.

Implications for drug development

DILI is a major cause of the withdrawal of potentially valuable therapies post-marketing (80). Current methods have not been shown to be helpful in predicting DILI or DI-ALH in clinical studies (81). Due to the lack of effective biomarkers, Hy's law is currently the most commonly used tool available to the pharmaceutical industry for assessing a drug's potential to cause severe DILI. Therefore, the most specific indicator that a definite drug is hepatotoxic is the occurrence of drug-induced hepatocellular injury with jaundice, and/or an increased International Normalized Ratio (INR) (82). Labelling cases as potential DI-ALH in clinical trials may trigger follow-up actions, including: determining liver-specific autoantibodies in patients with elevated aminotransferases, administering steroids according to current recommendations for treatment of AIH, and long-term follow-up of study subjects to monitor for possible flares of AIH in either the presence or absence of study drug. For this reason, caution should be exerted in classifying a case of suspected DILI as DI-ALH, since this can have a profound impact on the workup of these patients, the decision to interrupt or discontinue treatment and the overall safety

assessment of the developmental compound. A comprehensive identification of potential DI-AILH cases in clinical studies would require a dedicated initiative, for instance in the frame of a public-private partnership that specifically addresses this question and allows partner companies to share samples and data.

A much better understanding of the mechanisms underlying DILI and DI-ALH is essential to design new improved predictive models (82). Thus, future research should focus on applying new technological advances and constructing a systematic biological approach to understand the mechanism and identify initial pathways. This will allow the identification of new treatment targets and other environmental and genetic factors that also have a profound impact on the risk of an individual patient developing overt liver disease. This would allow physicians to stratify their patients according to their environmental and genetic factors and to adopt a personalized medicine approach for the treatment of DI-ALH.

Current gaps and future steps of research to improve the analysis and management of DI-ALH

Several gaps were identified in terms of clinical diagnosis and management which benefit future research on the mechanisms of prevention and treatment of DI-ALH. The participants reached a consensus regarding existing gaps in the field motivating more research.

- To define the precise epidemiology of DI-ALH, a correct diagnosis of the (auto)immune phenotype of DILI is necessary. Comprehensive identification of potential DI-ALH cases in clinical studies would require a dedicated initiative, preferably prospective studies that specifically addresses this question and allows partner companies to share samples and data.

- The use of a consensus definition of DI-ALH will allow analyses of larger populations based on the same criteria, to define the different classes of drugs/agents that can cause DI-ALH as an entity, for better understanding of the outcome and management of patients.
- There is lack of data and specific biomarkers to characterise and discriminate DILI vs AIH vs DI-ALH. It is imperative to improve liver histology evaluation to better characterize the patterns of DI-ALH. The experts agree on the need to develop a tool for diagnosing DI-ALH before the initiation of therapy.
- A systematic investigation of the type and pattern of autoantibodies detected in DI-ALH, adhering to dedicated methodological guidelines, with comparison to AIH is warranted to investigate whether they can serve as specific biomarkers for diagnosis, prognosis and response to treatment.
- The experts agree that information on the morphologic evaluation of liver biopsy can be augmented by using immunohistochemical and molecular techniques. Future studies incorporating immune cell phenotyping may help identify immunohistochemical markers useful for the diagnosis of DI-ALH. A properly designed biopsy study and the discovery of new molecular markers that can explore these options may provide clarity in the differentiation of DI-ALH and AIH.
- Testing for carriage of particular HLA alleles in selected cases will assist in the diagnosis of DILI or AIH. Further studies are needed to clarify AIH and DI-ALH genetic heterogeneity and pathogenesis. Moreover, there is a clear need for evaluating the use and effectiveness of genetic tests in the diagnosis and decision-making in the clinical context of AIH vs DI-ALH.
- The current identified gaps in the management of DI-AILH are: 1) which patients require immunosuppression, 2) standardization in treatment regimens such as dose

and duration of therapy in the event immunosuppression is administered and 3) when to withdraw therapy. Thus, a set of criteria for DI-ALH assessment including tests and follow-up that should be done in prospective studies has been recommended in the workshop (Table 5).

- A prospective assessment of predictors of positive rechallenge with the same or with a different drug and outcomes should be performed.
- Liver biopsies and conducting spatial profiling of gene signatures between DI-ALH and AIH would highlight the difference for future fine-tuning of nomenclature. Future research involving comparative analysis using distinct "omics" technologies may allow for categorizing DI-ALH cases to better predict their progression, spontaneous resolution, response to therapy and outcomes.
- The experts agreed that larger prospective studies with relevant follow-up information on immunosuppression are needed to properly characterize the natural history of DI-ALH. Moreover, since the progression of DI-ALH to ALF is uncommon, and there are no biomarkers predictive of disease progression, the experts recommend that patients with acute severe presentation should be referred and managed in centres with advanced hepatology care.

DI-ALH Management: Developing Guidelines

The lack of a reliable diagnostic biomarkers and evidence-based treatment paradigm has resulted in limited guidance on how to manage this aspect of DILI (2,25-27). DI-ALH was defined in the EASL Clinical Practice guideline (CPG) as "acute DILI with serological and/or histological markers of *idiopathic* AIH" (2).

Conclusions

In summary, DI-ALH as a clinical phenotype is poorly characterized. Establishing new collaborative initiatives will allow for a better understanding of the various DILI signatures. The term DI-ALH was preferred by the majority of experts to describe this clinical and biochemical phenotype. Closing this gap should be the primary focus of future collaborative research to advance this field, with the ultimate goal of developing novel targeted risk management and therapeutic strategies to optimally manage DILI, AIH and DI-ALH, using precision medicine approaches.

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"Author names in bold designate shared co-first authorship"

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LEGEND TO FIGURES

Figure 1. Liver biopsy findings in DI-ALH. (A) A biopsy of minocycline-related DI-ALH shows a chronic hepatitis pattern of injury with predominantly portal based inflammation and periportal fibrosis. Interface hepatitis is noted (arrows). (B) Higher magnification shows plasma cells aggregated at the interface. (C) A biopsy of nitrofurantoin-related DI-ALH demonstrates an acute hepatitis pattern of injury with predominantly lobular inflammation and perivenular confluent necrosis (arrow). (D) High magnification shows enlarged hepatocytes with cytoplasmic vacuolation, multinucleation and emperipolesis, against the background of lymphoplasmacytic infiltration.

Figure 2. Overlap between Drug-Induced liver injury (DILI), Drug-induced autoimmune-like hepatitis (DI-ALH) and idiopathic Autoimmune hepatitis (AIH). Limited number of DI-ALH patients progress into chronicity and evolve disease phenotype to more of an idiopathic AIH type.

Figure 3. An algorithm to approach suspected DI-ALH in clinical practice.

*****Alternatively, in mild cases associated with specific drugs known to induce this phenotype (i.e. infliximab) with clinical/biochemical improvement a liver biopsy would not always be necessary

Table 1. Key challenges faced in detecting, assessing, and managing suspected acute drug-induced liver injury with the autoimmune phenotype (DI-ALH) to distinguish from idiopathic autoimmune hepatitis (AIH).

1. The literature surrounding DILI with autoimmune phenotype is scarce but its awareness is increasing
2. There are no regulatory guidelines or society position papers that systematically address case definitions, diagnostic approaches and management in patient with suspected DI-ALH. It is difficult to differentiate between different phenotypes with certainty.
3. Both diagnoses are reliant on a number of overlapping clinical features. Diagnosis of DILI as well as AIH are dependent upon the systematic evaluation of clinical, laboratory and histological features. While increasing evidence points to the involvement of immune mechanisms in DILI, drugs and herbals and dietary supplements (HDS) with positive autoantibody titers exhibit a pattern of injury closely simulating AIH, presenting many or all of the features of classical AIH.
4. In a few patients, episodes of DILI have developed from multiple drugs (recurrent DILI) and second episodes of DILI were more likely to be associated with features of AIH.
5. It is plausible that drugs and vaccines can trigger AIH and yet, there are not sufficiently robustly designed studies to identify particular agents that induce such an event. Some drugs have well-documented cases of DI-ALH, whereas some suspected are probably innocent bystanders but this is a dynamic process with evolving new drugs.
6. It is unknown if patients with DI-ALH tend to resolve spontaneously or can even evolve to acute liver failure as idiopathic AIH occasionally does.
7. Liver biochemical monitoring and stopping criteria that are utilized for patients with no underlying liver disease who develop a hepatocellular or cholestatic DILI signal in the setting of a clinical trial may not apply to those with DILI and autoimmune phenotype.
8. Management of DI-ALH with immunosuppressants is controversial and not evidence-based. It is questionable how long the clinician should wait before initiating immunosuppression (usually corticosteroids) when liver tests do not improve and even worsen after the discontinuation of the implicated agent. There is no guidance on when to start immunosuppressive therapy, which dose, how long it should be maintained, or if and when it needs to be discontinued.

Table 2. Summary of case series of patients with DI-ALH and response to treatment

Observational studies	Björnsson 2010[14] (n=24)	Ghabril 2013[35] (n=6)	Rodrig. 2015[34] (n=8)	De Boer 2017[24] (n=88)	Björnsson 2017[17] (n=15)	Björnsson 2022[50] (n=36)	García-Cortés 2023[51] (n=33)
Drugs implicated (number of patients)	Nitrourantoin (10) Minocycline(10) Cephalexin (1) Prometrium (1)	Infliximab (3) Etanercept (2) Adalimumab	Infliximab (7) Adalimu-mab	Nitrofuran-toin (42) Minocycline (28) Methyldopa (10) Hydralazine (7)	Infliximab (10) Nitrofuran-toin (3) Imatinib	Infliximab (31)	Statins (8) Nitrofurantoin.. (5) Minocycline (4) Amox-Clav (2) Cyproterone (2) Others (11)
Age (y), median (range)	53 (24-61)[¥]	35 (28-54)	40 (34-69)	Nitrofurantoin 65 (36-84) Minocycline 19 (16-61) Methyldopa 29 (18-43) Hydralazine 60 (42-76)	55 (20-91)	46 (32-54)[¥]	Mean 53 (15-86)
Females %	92%	83%	63%	91%	93%	78%	58%
Autoimmune comorbidities, %	-	100%	100%	-	73%	-	27%
Acute onset, %	100%	100%	100%	100%	100%	100%	100%
Treatment duration (d), median (range)	-	-	-	-	116 (84-1320)	-	92 (40-312)[¥]
Time to onset (d), median (range)	-	112 (14-364)	-	277 (8-7032) 100 (13-1572)*	-	110 (94-144)[¥]	94 (42-255)[¥]
Jaundice, %	50%	50%	-	59%	53%	11%	58%
Type of liver injury, %	-	HC: 83% Mix: 17% Chol: 0%	-	HC: 74% Mix: 17% Chol: 9%	HC: 93% Mix: 7% Chol: 0%	HC: 64% Mix: 33% Chol: 3%	HC: 84% Mix: 9.7% Chol: 6.3%
Hypersens. features, %	-	Fever: 16%	-	Fever: 25% Rash: 26%. At least two features: 17%	-	No fever, no rash	Fever: 6% Rash: 3%
% with peripheral eosinophilia	-	0%	-	4.5%	-	8%	18%
% with autoimmune features	100%	50%	100%	72%	93%	69%	100%
High IgG values, %	90%	-	75%	39%	40%	17%	58%[†]
Corticosteroids: dose/duration	20-40 mg x 8 weeks	-	-	-	20-40 mg x 8 weeks	20-40 mg x8 weeks	-
Response to suspension of drug and steroids (number)	100% Spont. (14) steroids (12)	100% Spont. (1) steroids (5)	100% Steroids (8)	100% Spont (47) steroids (41)	100% Spont. (6) steroids (9)	100% Spont (19) steroids (17)	100% Spont. (13) steroids (20)
Relapse after corticosteroid withdrawal	0%	0%	0%	-	0%	0%	12%
Cirrhosis at presentation	0%	16%	13%	4.5%, at follow-up	0%	-	6%

Abbreviations: AIH: autoimmune hepatitis. Amox/Clav: amoxicillin/clavulanate; Chol: cholestatic; d: days; HC: hepatocellular; IgG: immunoglobulin G; Mix: mixed; Hypersens: hypersensitivity; Spont: spontaneous; y: years; *: patients with and without autoimmune features, respectively. interquartile range (IQR). †: based on available data.

Table 3. Drugs with well documented DI-ALH (strong association), with convincing reports, that have been analyzed and undergone causality assessment; possible DI-ALH with several reports that suggest a relationship but do not fulfill criteria proposed in a recent paper on DI-ALH (24), those that have been reported, mostly in single reports, with short follow-up and/or important clinical information lacking. Finally, drugs suspected to have induced DI-ALH but only in the 1970s and 1980s, before the detection of hepatitis C and with competing causes often not excluded. References are in parentheses.

Highly probable drug and HDS association (n=18)	Possible drug association (n=4)	Reported but unproven (n=21)	Reported only in the 1970s and 1980s (n=15)
Nitrofurantoin (14)	Etanercept (21)	Cephalexin (14)	Halothane (4)
Minocycline (14)	Efalizumab (21)	Clometacine (4)	Tienilic cacid (4)
Methyldopa (20)	Atovaquone/ Proguanil (84)	Echinacea (4)	Oxiphensation (4)
Hydralazine (20)	Turmeric (21)	Pemoline (4)	Sulfonamide (4)
Infliximab (35)		Ma Huang (21)	Propylthiouracil (4)
Interferon-α & β (21)		Prometrium (14)	Isoniazid (4)
Atorvastatin (20)		Hydroxycut (4)	Dantrolene (4)
Simvastatin (20)		Meloxicam (4)	Perhexiline maleate (4)
Fluvastatin (20)		Methotrexate (4)	Amiodarone (4)
Rosuvastatin (20)		N-Nitroso-fenfluramine (4)	Papaverine (4)
Imatinib (21)		Ambrisentan (4)	Benzarone (4)
Masitinib (21)		Glucosamine/chondroitin sulfate (4)	Terbinafine (4)
Adalimumab (21)		Camostat/benzbromarone (4)	Methylphenidate (4)
Diclofenac (21)		Xiang-tian-guo (4)	Bupropion (4)
Methylprednisolone (21)		Indometacin (4)	Olmesartan (4)
Cyproterone (4)		Varenicline (21)	
Khat (21)		Menotrophin (21)	
Tinospora cordifola (21,83)		Indometacin (4)	
		Fenofibrate (4)	
		Pazopanib (4)	
		Phenprocoumon (4)	

Table 4: Proportion of patients with AIH with positive auto-antibodies compared with their prevalence among healthy population. Auto-antibodies are compared with the proportion of those who are positive for genetic tests in both groups. Adapted from reference 2.

Test: antibodies	% positive in AIH cases	% positive in 'normal' population
ANA 1:60	68%-75%	15% (< 40 ♀) - 24% (> 40 ♀)
ASMA	52%-59%	Up to 43%
IgG >1600 mg/dL	86%	5%
Anti-LKM	4%-20%	1%

Abbreviations: AIH, autoimmune hepatitis; ANA, anti-nuclear antibody; anti-LKM, anti-liver-kidney-microsomal antibody; ASMA, anti-smooth muscle antibody; DILI, drug-induced liver injury; HLA, human leukocyte antigen; IgG, immunoglobulin

Table 5. Minimal elements for assessment of a suspected case of drug-induced autoimmune-like hepatitis (DI-ALH)

Demographics	age, sex, weight, BMI, ethnicity
Clinical Data	• Comorbid conditions, autoimmune disorders, underlying liver disease (e.g. steatosis) • Toxic habits: Alcohol, tobacco, illicit drugs, over the counter drugs. • Type of liver injury (aminotransferases, bilirubin, alkaline phosphatase) • Signes and Symptoms: jaundice, hypersensitivity features (rash, peripheral eosinophilia, lymphopenia), encephalopathy, ascites, hospitalization
Drug exposure history	• Take a thorough pharmacological history with exposure to drugs/vaccines/herbal remedies with doses and start-stop dates • Excluded exposure to immune-checkpoint inhibitors
Temporal relationship*	• Treatment duration, days • Latency, days
Meet criteria definition for DILI	• ALT exceeding 5 times ULN • ALP exceeding 2 times ULN • ALT exceeding 3 times ULN and bilirubin exceeding 2 times ULN
Exclusion alternative diagnosis[#]	Viral hepatitis A, B, C, and E, Biliary obstruction, Autoimmune hepatitis, Alcoholic hepatitis, Ischemic hepatitis, Malignancy
Biochemical parameters¶	• **Liver profile** at onset, on remission, when worsening, relapse (ALT, AST, ALP, Total Bilirubin, INR) • **Autoantibodies**: ANA, ASMA with pattern on kidney tissue, Anti-LKM1, anti-SLA/LP • **IgG levels**
Histological features	Date. Description of the following features recommended • Pattern of injury (portal or lobular based hepatitis) • Degree of necroinflammatory changes and fibrosis according to Ishak's grading and staging system (85) • Plasma cell infiltration or clusters. • Documentation of other histological features of significance: hepatocellular or canalicular cholestasis, chronic cholestasis changes, eosinophils, confluent necrosis, steatosis, vascular injury) • Exclusion of other diseases (e.g., steatohepatitis, cholangiopathy) • Overall assessment based on the revised AIH scoring system, simplified criteria, and histological criteria (3)
HLA data	Specific HLA for given drugs and general AIH related HLA
Severity**	As recommended for DILI nR based Hy's law
Treatment	• Steroid Therapy (when initiated)

	• Other immunosuppressant needed • Still on immunosuppressant
Outcome	• Remission achieved • Worsening of the disease • Relapse • Liver-related death • Liver transplant
Follow-up	2-4 weeks, 1-3-6-12-18-24 months after diagnosis and once a year thereafter for 5 years
Causality Assessment tools	• The RUCAM/CIOMS and its recently improved version RECAM. • The revised and the simplified AIH scoring systems issued by the International Autoimmune Hepatitis Group

*between drug exposure and injury onset and improvement

imaging studies needed

¶ measured at different times of follow-up

** as recommended by Aithal et al. [85].

ALT: Alanine transaminase; ULN: upper limit of normal; ALP:Alkaline phosphatase; ANA: anti-nuclear antibody, ASMA: anti-smooth muscle/anti-actin antibody, Anti-LKM1: anti-liver kidney-microsomal type 1 antibody, anti-SLA/LP: anti-soluble liver antigen/liver pancreas antigen; RUCAM/CIOMS: Roussel Uclaf Causality Assessment Method/Council of International Organization of Medical Sciences

Figure 1

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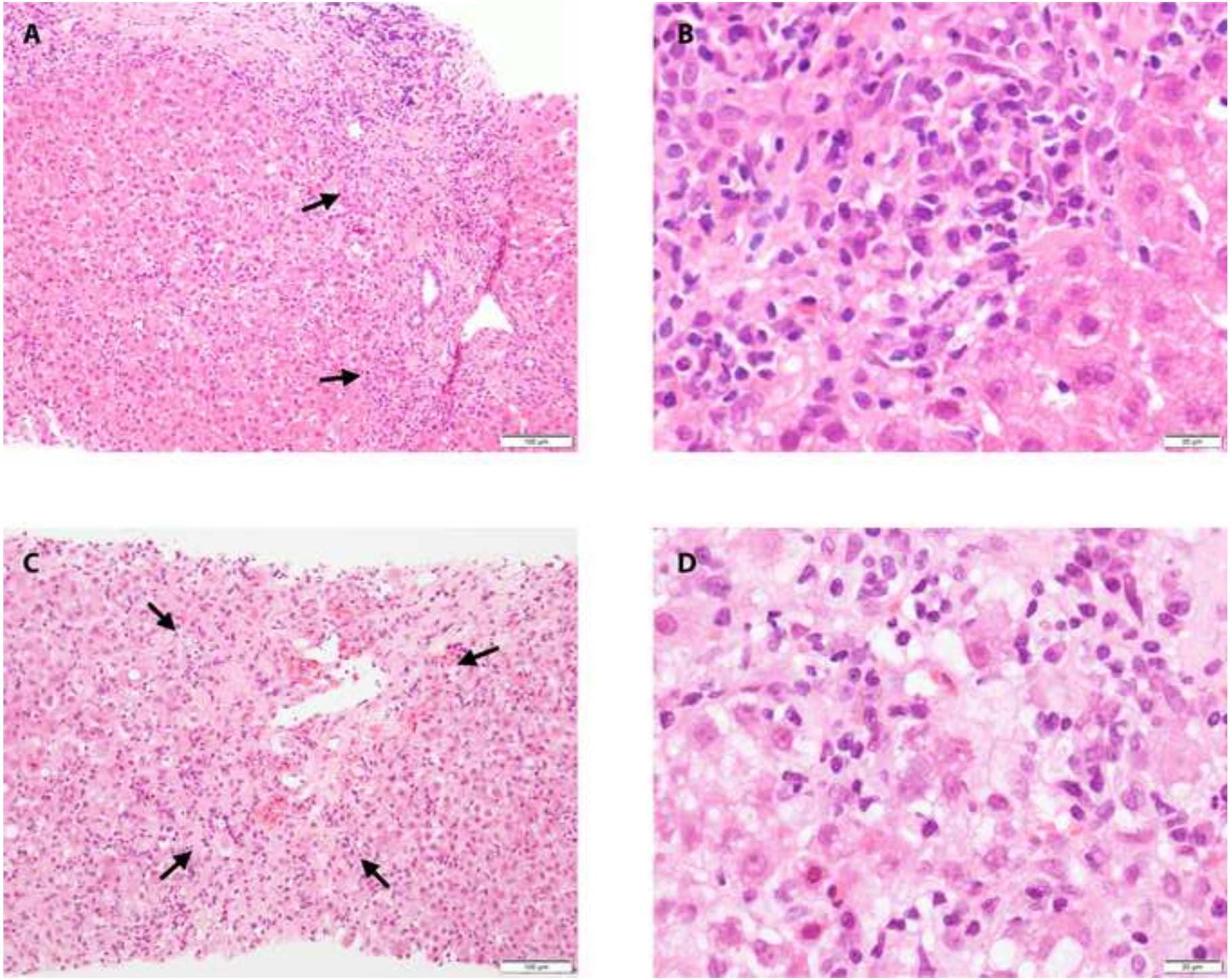

Figure

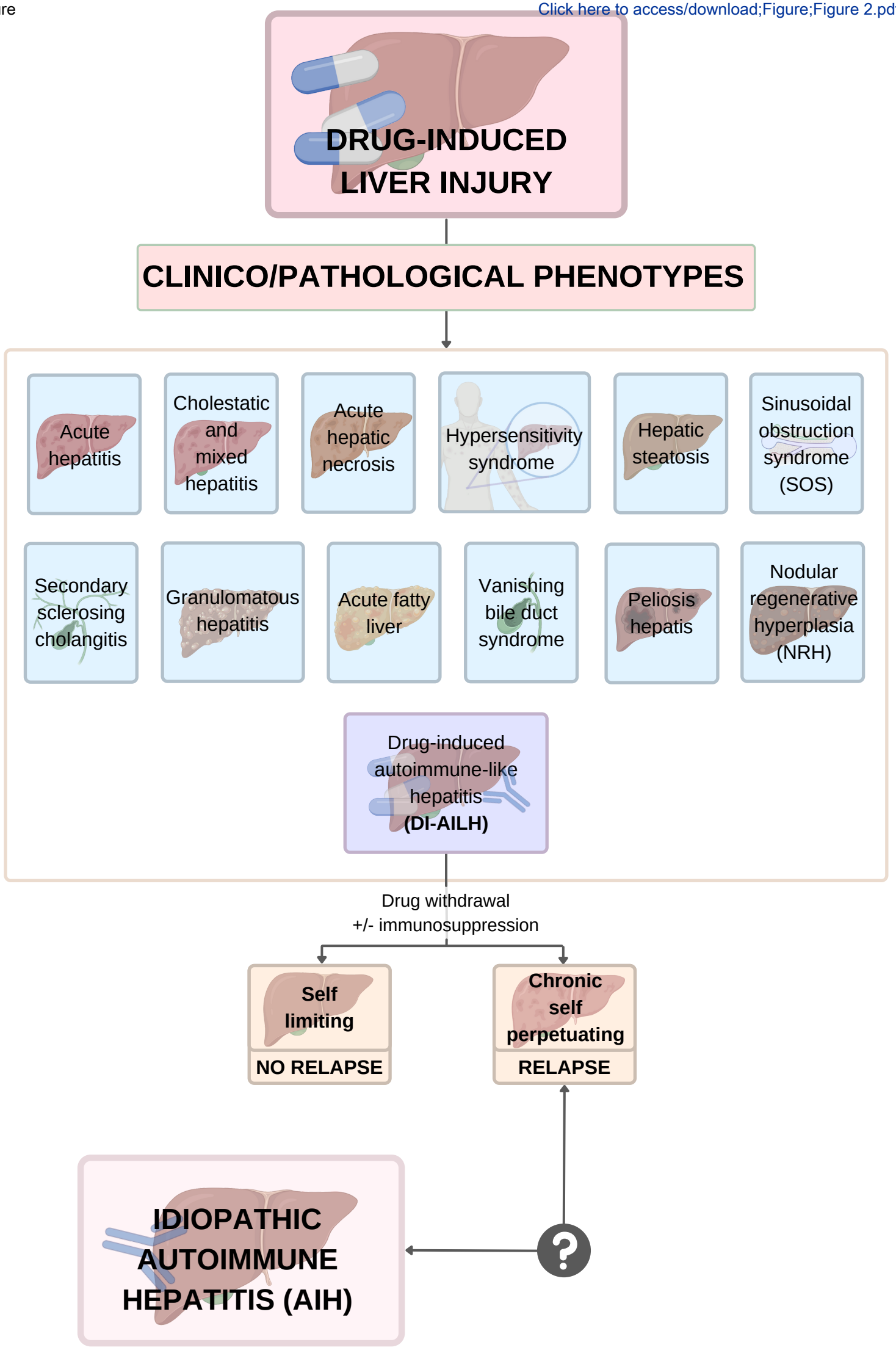

Figure 3