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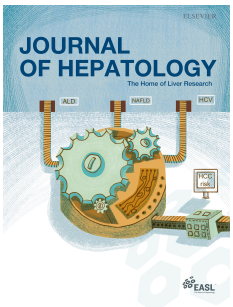

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Nomenclature, Diagnosis and Management of Drug-induced Autoimmune-like hepatitis (DI-ALH): An expert opinion meeting report

Raúl J. Andrade[1,2,*], Guruprasad P. Aithal[3*], Ynto S. de Boer[4*], Rodrigo Liberal[5*], Alexander Gerbes[6], Arie Regev[7] , Benedetta Terziroli Beretta-Piccoli[8], Christoph Schramm[9], David E. Kleiner[10], Eleonora De Martin[11], Gerd A. Kullak-Ublick[12], Guido Stirnimann[13], Harshad Devarbhavi[14], John M. Vierling[15] Michael P. Manns[16], Marcial Sebode[17], Maria Carlota Londoño[18,2], Mark Avigan[19], Mercedes Robles-Diaz[1,2], Miren García-Cortes[1,2], Edmond Atallah[3], Michael Heneghan[20], Naga Chalasani[21], Palak J. Trivedi[22], Paul H. Hayashi[23], Richard Taubert[24], Robert J. Fontana[25], Sabine Weber[26], Ye Htun Oo[27], Yoh Zen[28], Anna Licata[29], M Isabel Lucena[1,2,30,#], Giorgina Mieli-Vergani[31,#], Diego Vergani[31#] , Einar S. Björnsson[32#] on behalf of the IAIHG and EASL DHILI Consortium

[1]Servicio Aparato Digestivo and Servicio de Farmacología Clínica, Instituto de Investigación Biomédica de Málaga-IBIMA_Plataforma Bionand, Hospital Universitario Virgen de la Victoria, Universidad de Málaga, Málaga, Spain

[2]Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Madrid, Spain

[3]Nottingham Digestive Diseases Centre, Translational Medical Sciences, School of Medicine; NIHR Nottingham Biomedical Research Centre, Nottingham University Hospitals NHS Trust and the University of Nottingham, Nottingham, UK.

[4]Department of Gastroenterology and Hepatology, Amsterdam University Medical Centers, VU University Medical Center, Amsterdam, Netherlands.

[5]Gastroenterology Department, Centro Hospitalar Universitário de São João, Porto, Portugal; Faculty of Medicine of the University of Porto, Porto, Portugal.

[6]Department of Medicine II, LMU Klinikum Munich, Munich, Germany

[7]Eli Lilly and Company, Indianapolis, IN, USA

[8]Università della Svizzera Italiana, Facoltà di Scienze Biomediche. Epatocentro, Lugano, Switzerland

[9]Department of Medicine, University Medical Center Hamburg-Eppendorf. Hamburg Center for Translational Immunology. Martin Zeitz Center for Rare Diseases, University Medical Center Hamburg-Eppendorf, Hamburg, Germany.

[10]Laboratory of Pathology, National Cancer Institute, National Institutes of Health, Bethesda

[11]APHP, Hôpital Paul Brousse, Centre Hépato-Biliaire, INSERM Unit 1193, FHU Hepatinov, Villejuif, France.

[12]Department of Clinical Pharmacology and Toxicology, University Hospital Zurich, University of Zurich, Zurich, Switzerland.

[13]Department of Visceral Surgery and Medicine, Inselspital University Hospital and University of Bern, Bern, Switzerland.

[14]Department of Gastroenterology and Hepatology, St. John's Medical College Hospital, Bangalore, India.

[15]Departments of Medicine and Surgery, Section of Gastroenterology and Hepatology and Division of Abdominal Transplantation, Baylor College of Medicine, Houston, Texas, United States.

[16]Hannover Medical School, Centre of ERN RARE-LIVER, Hannover, Germany.

[17]Department of Internal Medicine, University Medical Center Hamburg-Eppendorf; European Reference Network on Hepatological Diseases (ERN RARE-LIVER), Hamburg, Germany

[18]Liver Unit, Hospital Clínic de Barcelona, Health Care Provider of the European Reference Network on Rare Liver Disorders (ERN-Liver), Institut d' Investigacions Biomédiques August Pi i Sunyer (IDIBAPS)

[19]Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, US Food and Drug Administration, Silver Spring, Maryland, USA

[20]Institute of Liver Studies, King's College Hospital, London, UK.

[21]University School of Medicine & Indiana University Health, Indianapolis, Indiana, USA.

[22]NIHR Birmingham BRC, Institute of Immunology and Immunotherapy, Centre for Liver and Gastrointestinal Research; Liver Unit, University Hospitals Birmingham National Health Service Foundation Trust Queen Elizabeth; Institute of Immunology and Immunotherapy; Institute of Applied Health Research, University of Birmingham, Birmingham, UK.

[23]Division of Hepatology and Nutrition, Food and Drug Administration, Silver Spring, Maryland, USA.

[24]Department of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Hannover, Germany. European Reference Network on Hepatological Diseases (ERN RARE-LIVER).

[25]Division of Gastroenterology and Hepatology, University of Michigan Medical School, Ann Arbor, MI, United States

[26]Department of Medicine II, LMU Klinikum Munich, Munich, Germany

[27]Center for Liver and Gastro Research & National Institute of Health Research Birmingham Biomedical Research Centre, University of Birmingham; Centre for Rare Disease and ERN Rare Liver Centre, Liver Transplant and Hepatobiliary Unit, University Hospital Birmingham NHS Foundation Trust, UK.

[28]Institute of Liver Studies, King's College Hospital, London SE5 9RS, UK.

[29]Medicina Interna ed Epatologia, Università degli Studi di Palermo, Palermo, Italy

[30]Platform ISCiii for Clinical Research and Clinical Trials SCReN UICEC- IBIMA, Málaga, Spain

[31]MowatLabs, Faculty of Life Sciences and Medicine, King's College London, King's College Hospital, London, United Kingdom

[32]Faculty of Medicine, University of Iceland, Department of Gastroenterology and Hepatology, Landspitali University Hospital, Reykjavik, Iceland

*co-first authors

[#]shared senior authorship

CORRESPONDING AUTHORS

Raul J Andrade
Medicine Department
School of Medicine
Boulevard Louis Pasteur 32,
Universidad de Málaga,
29071 Málaga, Spain.
Tel.: +34-952-131615;
andrade@uma.es

M Isabel Lucena
Pharmacology Department
School of Medicine
Boulevard Louis Pasteur 32,
Universidad de Málaga,
29071 Málaga, Spain.
lucena@uma.es

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Enrique del Campo (Instituto de Investigación Biomédica de Málaga y Plataforma en Nanomedicina-IBIMA Plataforma BIONAND; UGC de Aparato Digestivo, Hospital Universitario Virgen de la Victoria; Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Málaga, Spain.), Agustin Castiella (Gastroenterology Department, Donostia University Hospital, San Sebastian, Spain), Mar Riveiro-Barciela & Maria Buti (Liver Unit, Internal Medicine Department, Hospital Universitari Vall d'Hebron, Barcelona, Spain), Dermot Gleeson (Liver Unit, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK), Jessica Dyson (Freeman Hospital, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK), London, UK), Rosa Miquel (Institute of Liver Studies, Kings College Hospital, Denmark Hill, London, UK), Amber Bozward (Center for Liver and Gastro Research & National Institute of Health Research Birmingham Biomedical Research Centre, University of Birmingham; Centre for Rare Disease and ERN Rare Liver Centre, Liver Transplant and Hepatobiliary Unit, University Hospital Birmingham NHS Foundation Trust, UK.), Nelia Hernandez (Hospital de Clinicas, Montevideo, Uruguay), Averell H. Sherker, Jay H. Hoofnagle, Katrina Loh (National Institute of Diabetes and Digestive and Kidney Disease, National Institutes of Health, Bethesda, Maryland, USA), Ayako Suzuki (Duke University Medical Center, Durham, NC, USA), John M. Vierling (Baylor College of Medicine, Houston, Texas, USA), Mariana Cardoso (Johns Hopkins HospitaL, USA), Yimin Mao (Division of Gastroenterology and Hepatology, Shanghai Institute of Digestive Disease, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China), Elena Gómez Dominguez (Servicio de Aparato Digestivo, Hospital Universitario 12 de Octubre, Madrid, Spain).

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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

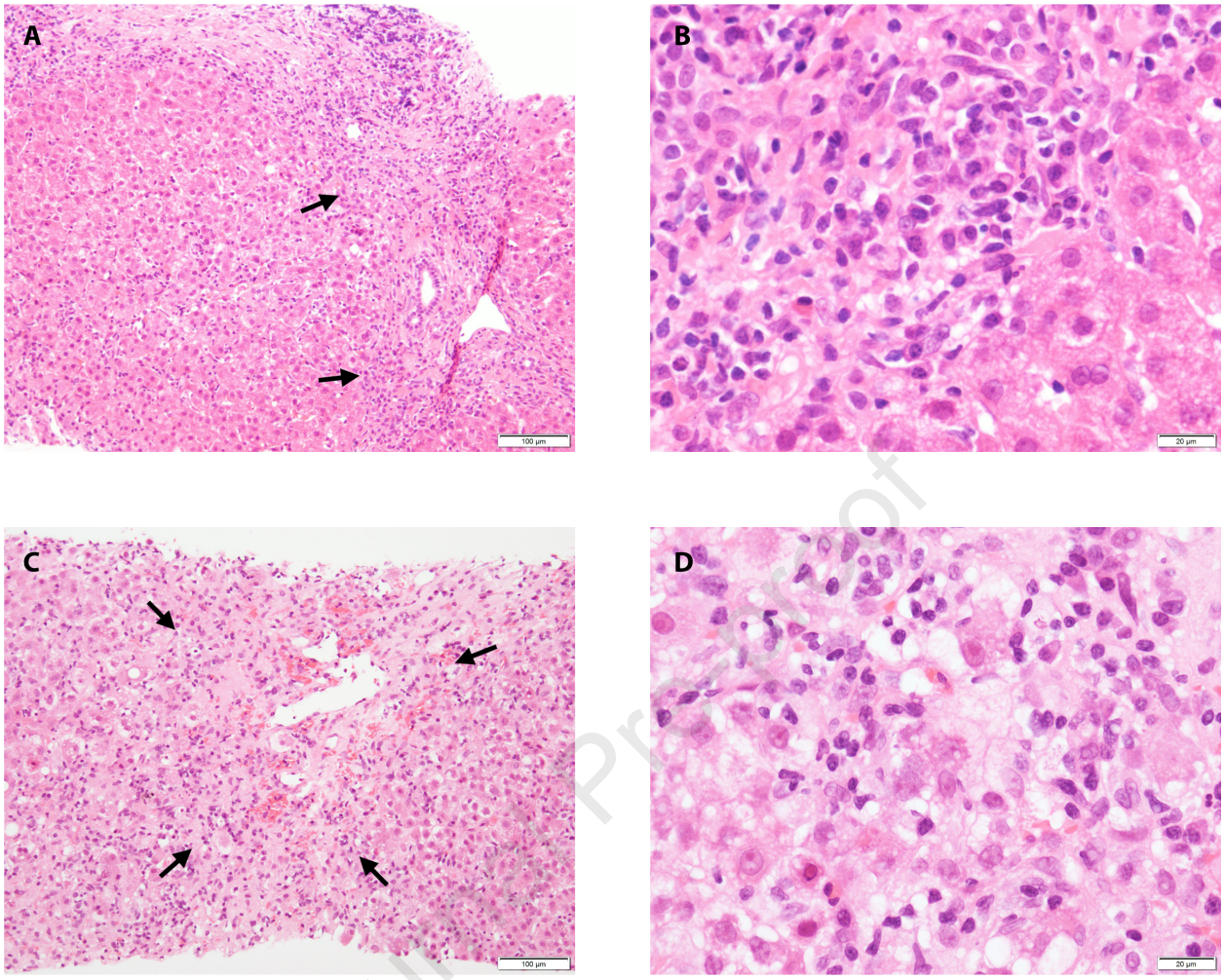
*between drug exposure and injury onset and improvement

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



DRUG-INDUCED LIVER INJURY

CLINICO/PATHOLOGICAL PHENOTYPES

- Acute hepatitis
- Cholestatic and mixed hepatitis
- Acute hepatic necrosis
- Hypersensitivity syndrome
- Hepatic steatosis
- Sinusoidal obstruction syndrome (SOS)
- Secondary sclerosing cholangitis
- Granulomatous hepatitis
- Acute fatty liver
- Vanishing bile duct syndrome
- Peliosis hepatis
- Nodular regenerative hyperplasia (NRH)
- Drug-induced autoimmune-like hepatitis **(DI-AILH)**

Drug withdrawal
+/- immunosuppression

- **Self limiting** → **NO RELAPSE**
- **Chronic self perpetuating** → **RELAPSE**

IDIOPATHIC AUTOIMMUNE HEPATITIS (AIH) ?