MÁSTER EN HEPATOLOGÍA

UAM Universidad Autónoma de Madrid

Universidad de Alcalá

Asignatura: Problemas clínicos y controversias en hepatología

"DILI autoinmune "

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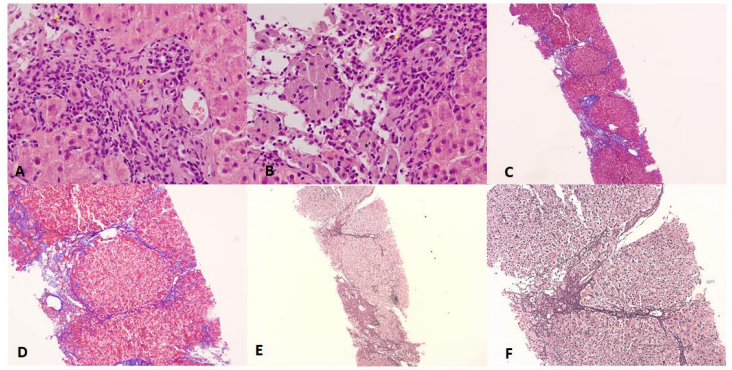
Hospital Universitario Virgen de la Victoria-IBIMA, Universidad de Málaga, CIBERehd

Clinical vignette

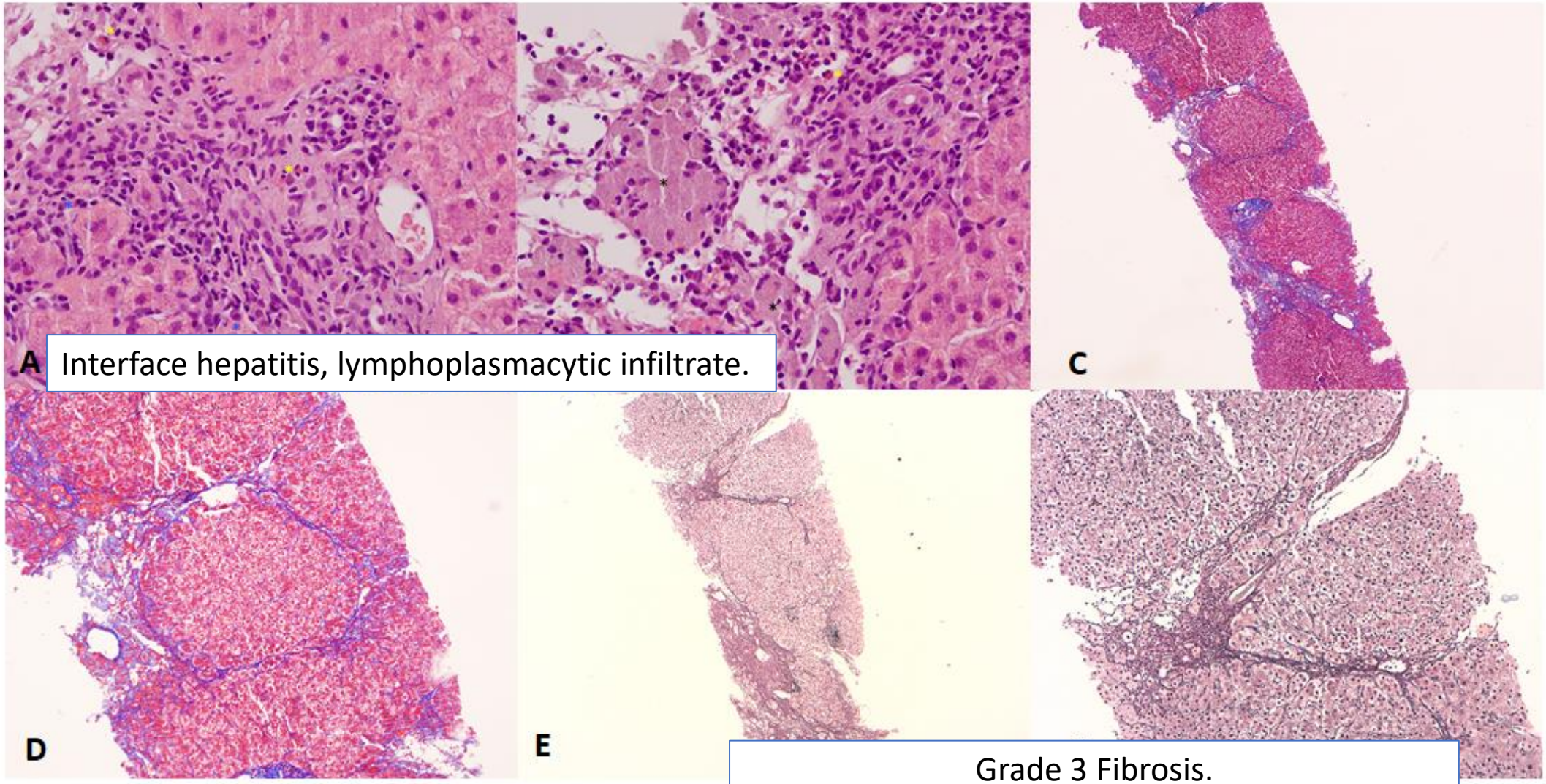
- 77 yr female
- Malaise, scleral icterus nausea and vomiting 4 days after
- SARS CoV-2 vaccine **Pfizer-BioNTech BNT162b** 2nd dose
- Bil T 3.1 mg/dL
- ALT 552 U/L
- INR 1.1
- ANA 1:160, AMA M2 +
- IgG 10.2 (6-15)
- DR4 (+)

- HAV, HBV, HCV, HEV, CMV, EBV, abdominal ultrasound, CT scan and Cholangio MRI normal
- After an initial improvement in liver test, a flare-up occurred, so a liver biopsy was performed



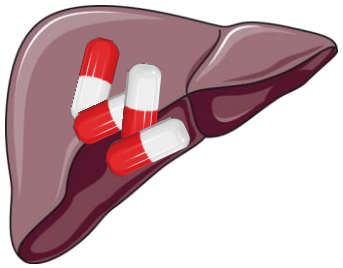
- Tapering prednisone 60 mg/d was initiated with normalization of liver tests.
- Azathioprine was not tolerated and budesonide was started
- 3 months later cerebral aspergillosis **death**

Liver biopsy



Interface hepatitis, lymphoplasmacytic infiltrate.

Grade 3 Fibrosis.



Drug induced liver injury

Acute hepatitis

Cholestatic and mixed hepatitis

Peliosis hepatis

Acute hepatic necrosis

Hypersensitivity syndrome

Hepatic steatosis

Sinusoidal obstruction syndrome (SOS)

Secondary sclerosing cholangitis

Granulomatous hepatitis

Acute fatty liver

Vanishing bile duct syndrome

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)

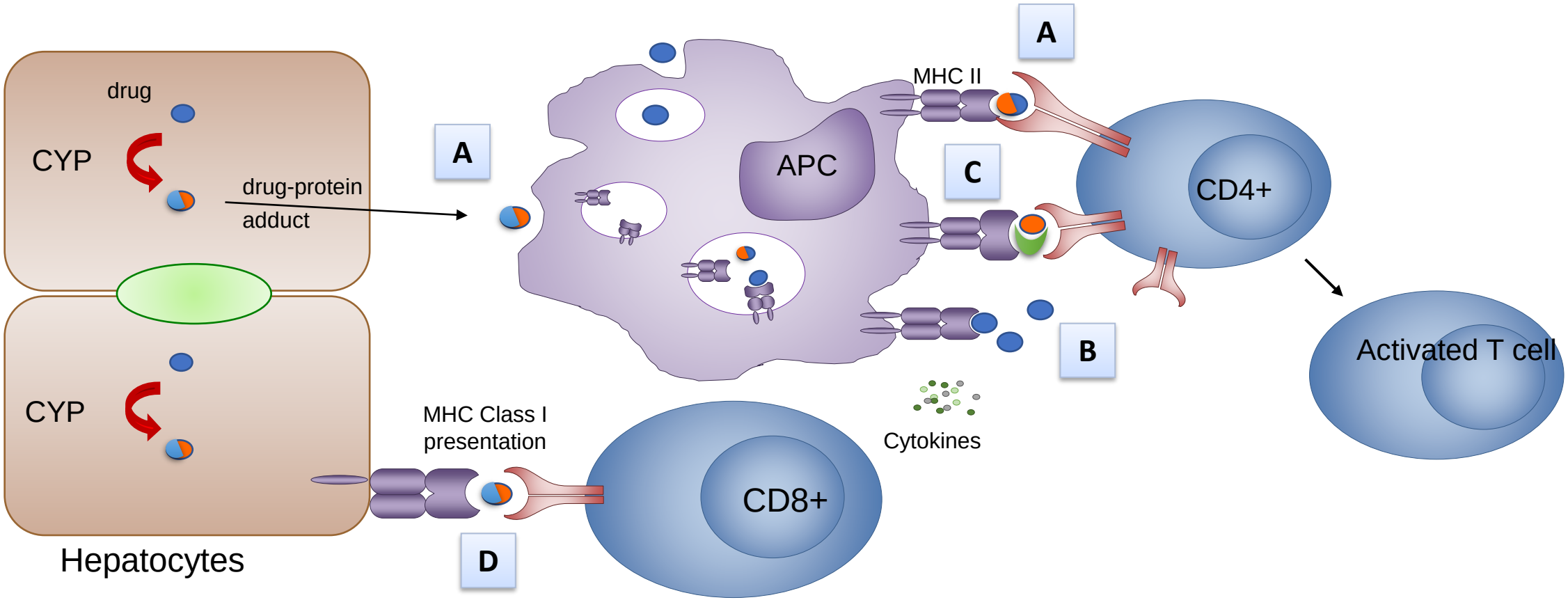
Andrade RJ et al., *J Hepatol.* 2023: May 8:S0168-8278(23)00320-3. doi: 10.1016/j.jhep.2023.04.033.

DILI autoinmune

- Es un fenotipo de hepatitis autoimmune que se cree que un fármaco ha podido iniciar
- Identificación en aumento en la literatura
- No hay criterios diagnósticos unanimemente aceptados (algunos autores no aceptan su existencia)
- Su frecuencia depende del contexto donde se identificó
  - En bases de datos retrospectivas de HAI (9%- 13%)
  - In registros prospectivos de DILI (2%)
- Algunos fármacos tienen mayor tendencia que otros a producer un fenotipo autoimmune:
  - Minociclina, nitrofurantoina
- Factores de riesgo de presentación autoimmune del DILI independientemente del fármaco responsable:
  - 2º episodio de DILI por otro fármaco
  - DILI de evolución crónica
  - Enfermedades autoimmunes pre-existentes

Björnsson et al, *J Hepatol* 2009 50: 511–7. Björnsson et al. *Hepatology* 2010; 51: 2040–8.
Lucena,.., Andrade RJ. *J Hepatol* 2011; 55: 820–7.
Yeong et al, *Hepatol Res* 2015; doi: 10.1111/hepr.12532

The immune response: CD4+/ CD8+ T cells



Kullak-Ublick GA, Andrade RJ et al. *Gut* 2017:66(6):1154-1164

ACG (DILI) 2014

- «In individuals with suspected hepatocellular or mixed DILI:

… (a) acute viral hepatitis and **autoimmune hepatitis should be excluded.** ***Strong recommendation, very low level evidence***

- «A liver biopsy should be considered **if autoimmune hepatitis remain a competing etiology and if immunosupressive therapy is contempleted**. ***Strong recommendation, low level of evidence***

ACG (DILI) 2021

...«**it,s well known that some medications have high propensity to cause autoimmune-like DILI** (e.g minocycline, nitrofurantoin). Serum autoantibodies (ANA and ASMA) and immunoglobulin G levels should be routinely obtained, and a liver biopsy may be considered in selected cases.»

...«immunosupressants can eventually be stopped without inciting a flare-up of AIH, **whereas idiopathic AIH most patients will experience flare-ups when immunosuppresants are stopped»**

Chalasani NP, et al Am J Gastroenterol 2014; 109:950-66; Chalasani NP, et al Am J Gastroenterol 2021; 116:878-898.

ARTICLE IN PRESS

Clinical Practice Guidelines

JOURNAL OF HEPATOLOGY

EASL Clinical Practice Guidelines: Drug-induced liver injury☆

European Association for the Study of the Liver*

April 2019 | **Topic:** Metabolism, alcohol and toxicity

Drug-induced liver injury

Idiosyncratic (unpredictable) drug-induced liver injury is one of the most challenging liver disorders faced by hepatologists, because of the myriad of drugs used in clinical practice, available herbs and dietary supplements with hepatotoxic potential, the ability of the condition to present with a variety of clinical and pathological phenotypes and the current absence of specific biomarkers.

Read More >

☆ **Clinical practice guidelines panel:** Chair: Raul J. Andrade; Panel members: Guruprasad P. Aithal, Einar S. Bjornsson, Neil Kaplowitz, Gerd A. Kullak-Ublick, Dominique Larrey; EASL Governing Board representative: Tom H. Karlsen.

Special phenotypes: AIH

- A number of drugs have been associated with the syndrome drug-induced AIH that shares many features of idiopathic AIH

Recommendations	Grade of evidence	Grade of recommendation
• Drug-induced AIH should be distinguished from idiopathic AIH on detailed evaluation including causality assessment, serological, genetic tests and liver biopsy whenever possible.	Extrapolation Level 1 studies	B
• In patients with suspected drug-induced AIH and treated with immunosuppressant, withdrawal of therapy once the liver injury has resolved should be accompanied by close monitoring.	Level 2a studies	B

EASL CPG DILI J Hepatol 2018;

EASL(AIH) 2015

- «The relationship between DILI and AIH is complex and not fully understood». ***No recommendations***

AASLD (AIH) 2019

«DILI can mimic AIH and an unpredictable idiosyncratic or hypersensitivity drug reaction has been implicated in 2-17% of patients with classical features of AIH»

…«The histological findings …are similar to those of classical AIH, except for the absence of advanced fibrosis or cirrhosis in most instances»…

Guidance statments

- Drug induced-liver injury AIH-like liver injury must always be considered in the differential diagnosis of AIH
- The offending agent must be withdrawn and monitoring maintained to ensure laboratory resolution
- Glucocorticoid therapy for DILI-AIH-like injury should be instituted when symptoms or disease activity are severe (e.g fulfill Hy,s law) or if symptoms and laboratory tests fail to improve or worsen after discontinuation of the offending drug
- Laboratory flare after glucocorticoid withdrawal suggets underlying AIH and the need for immunosupresive therapy. ***No established grade of recommendation***

EASL Clinical Practice Guidelines: Autoimmune hepatitis. J Hepatol. 2015;63:971-1004; Mack CL, et al. AASLD Guidance. Hepatology 2020;72:671-722

Received: 20 January 2022 | Accepted: 25 March 2022

DOI: 10.1002/hep4.1959

ORIGINAL ARTICLE

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

Einar S. Björnsson[1,2] | Inmaculada Medina-Caliz[3] | Raul J. Andrade[3,4] | M. Isabel Lucena[3,4]

- Search was undertaken in pubmed (pubmed.ncbi.nlm.nih.gov) on “drug-induced autoimmune hepatitis” as well as “herbal medicine” AND “autoimmune hepatitis” until 2021.
- Published case reports and case series on suspected DI-AIH analyzed.
- DI-AIH due to nitrofurantoin, methyldopa, hydralazine, minocycline and infliximab were excluded and liver injury associated with check point inhibitors

Criteria of “drug induced autoimmune hepatitis” for case reports/case series

- (1) Drug as a potential trigger of liver injury with autoimmune features and histological findings compatible with AIH.
- (2) No or incomplete recovery or worsening of liver tests after discontinuation of the drug,
- (3) Corticosteroids requirement or spontaneous recovery
- (4) Follow-up without immunosuppression (IS) and no relapse of AIH at least 6 months after discontinuation of IS.
- (5) Drugs potentially inducing autoimmune-like hepatitis with a chronic course

Possible if at least 3 out of 4 first criteria were met

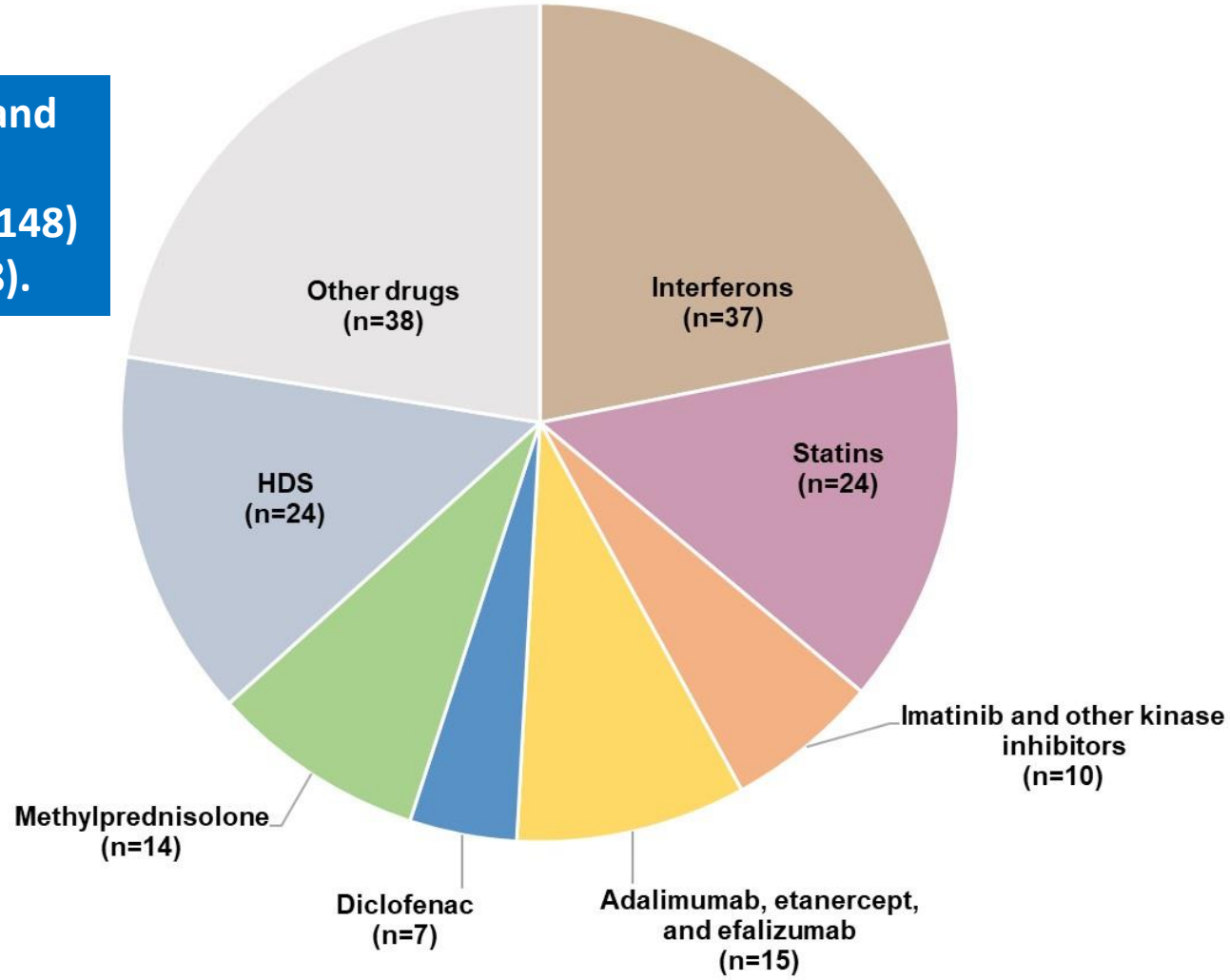
Probable if at least the 4 first criteria were met

Bjornsson E, Medina-Cáliz I, Andrade RJ Lucena MI. *Hepatology* Comm 2022; 6:1895-1909

;

Most commonly reported class of agents leading to DI-ALH

186 case reports identified and analyzed
- **conventional drugs (n=148)**
- **herbal medicines (n=38).**



Other drugs: oxyphenisatin, sulfamethoxypyridazin, propylthiouracil, dantrolene, perhexiline, clometacin, amiodarone, pemoline, meloxicam, moxifloxacin, omeprazole, ezetimibe/enalapril, olanzapine, metotrexate, bosentan, camostat/benzbromarone, papaverin, benzarone, terbinafine, methylphenidate, bupropion, indomethacin, enalapril/metformin, olmesartan/amlodipine, varenicline, menotrophin, and cyproterone acetate.

Bjornsson E, Medina-Cáliz I, Andrade RJ Lucena MI. *Hepatology Comm* 2022; 6:1895-1909

Received: 17 February 2023 | Revised: 9 May 2023 | Accepted: 11 May 2023

DOI: 10.1111/liv.15623

Liver INTERNATIONAL WILEY

ORIGINAL ARTICLE

Clinical presentation, causative drugs and outcome of patients with autoimmune features in two prospective DILI registries

Miren García-Cortés[1,2] | Aida Ortega-Alonso[1,2] | Gonzalo Matilla-Cabello[1] | Inmaculada Medina-Cáliz[1] | Agustín Castiella[3,4] | Isabel Conde[5] | Elvira Bonilla-Toyos[1,6] | José Pinazo-Bandera[1] | Nelia Hernández[7] | Martin Tagle[8] | Vinicius Nunes[9] | Raymundo Parana[10] | Fernando Bessone[11] | Neil Kaplowitz[12] | M. Isabel Lucena[1,2,6] | Ismael Alvarez-Alvarez[1,2,6] | Mercedes Robles-Díaz[1,2] | Raúl J. Andrade[1,2]

1) fulfilling the biochemical criteria for DILI after ruling out alternative causes of liver disease and having had exposure to a potentially hepatotoxic drug; 2) no underlying liver disease before taking the suspected drug; 3) intake of a drug prior to the onset of the liver damage. Two or three of the following were required: positive autoantibodies (antinuclear [ANA], anti-smooth muscle [ASMA], and/or anti-liver kidney microsomal type 1 [LKM1]), increased immunoglobulin G (IgG) levels above ULN, or liver biopsy with features of AIH, including interface hepatitis, portal/periportal lymphoplasmacytic and eosinophilic infiltration.

DILI with and without autoimmune features vs acute autoimmune hepatitis (AIH) cases

	DILI without autoimmune features (n=1,393)	DILI with autoimmune features (n=33)	AIH (n=43)†	*p* value
Female sex, n (%)	732 (53)	19 (58)	29 (67)	0.138
Age (y), mean±SD (range)	52±18 (11-91)	53±20 (15-86)	55±16 (19-80)	0.586
Diabetes, n (%)	142 (10)	3 (9.1)	0 (0)	**0.046**
Hypertension, n (%)	278 (20)	10 (30)	4 (9.3)	0.067
Dyslipidaemia, n (%)	152 (11)	8 (24)	NA	**0.025**
Pattern of liver injury, n (%)				**0.005**
Hepatocellular	818 (63)	26 (84)	35 (81)	
Cholestatic	267 (21)	2 (6.5)	1 (2.3)	
Mixed	213 (16)	3 (9.7)	7 (16)	
Time to onset (d), median (IQR)	25 (10-62)	94 (42-255)	NA	**<0.001**
Liver profile at recognition (x ULN), median (IQR)				
Total bilirubin	4.6 (1.1-10)	2.9 (1.5-6.6)	3.4 (1.2-7)	0.254
Aspartate aminotransferase (AST)	6.2 (2.9-18)[a,b]	20 (11-29)	20 (10-26)	**<0.001**
Alanine aminotransferase (ALT)	9.2 (4.6-23)[a,b]	22 (13-34)	19 (11-37)	**<0.001**
Alkaline phosphatase (ALP)	1.6 (1.0-2.6)	1.8 (1.0-2.6)	1.5 (1.1-2.0)	0.917

	DILI without autoimmune features (n=1,393)	DILI with autoimmune features (n=33)	AIH (n=43)†	*p* value
Immunoglobulin G (peak; g/L), mean±SD	13±7.0[a,b]	23±11	24±13	**<0.001**
Positive autoantibodies titres, n (%)	252 (18)	33 (100)	38 (88)	**<0.001**
ANA	164 (14)	30 (91)	30 (71)	**<0.001**
ASMA	111 (10)	11 (34)	19 (63)	**<0.001**
Anti-LKM1	9 (1.1)	1 (4.0)	4 (25)	**<0.001**
Immunosuppressive treatment, n (%)	69 (6.9)	21 (63)	43 (100)	**<0.001**
Normalization time (d), median (IQR)	93 (48-182)	162 (90-260)	NA	**0.004**

† Biochemical parameter values obtained at the closest time to diagnosis.

[a] Significant differences between cases of DILI without and with autoimmune features ($p<0.05$).

[b] Significant differences between cases of DILI without autoimmune features and AIH ($p<0.05$).

[c] Significant differences between cases of DILI with autoimmune features and AIH ($p<0.05$).

García-Cortés, Ortega-Alonso, Matilla-Cabello *et al*. *Liver Int*. 2023

Characteristics of DILI cases with autoimmune features based on immunosuppresion schedule

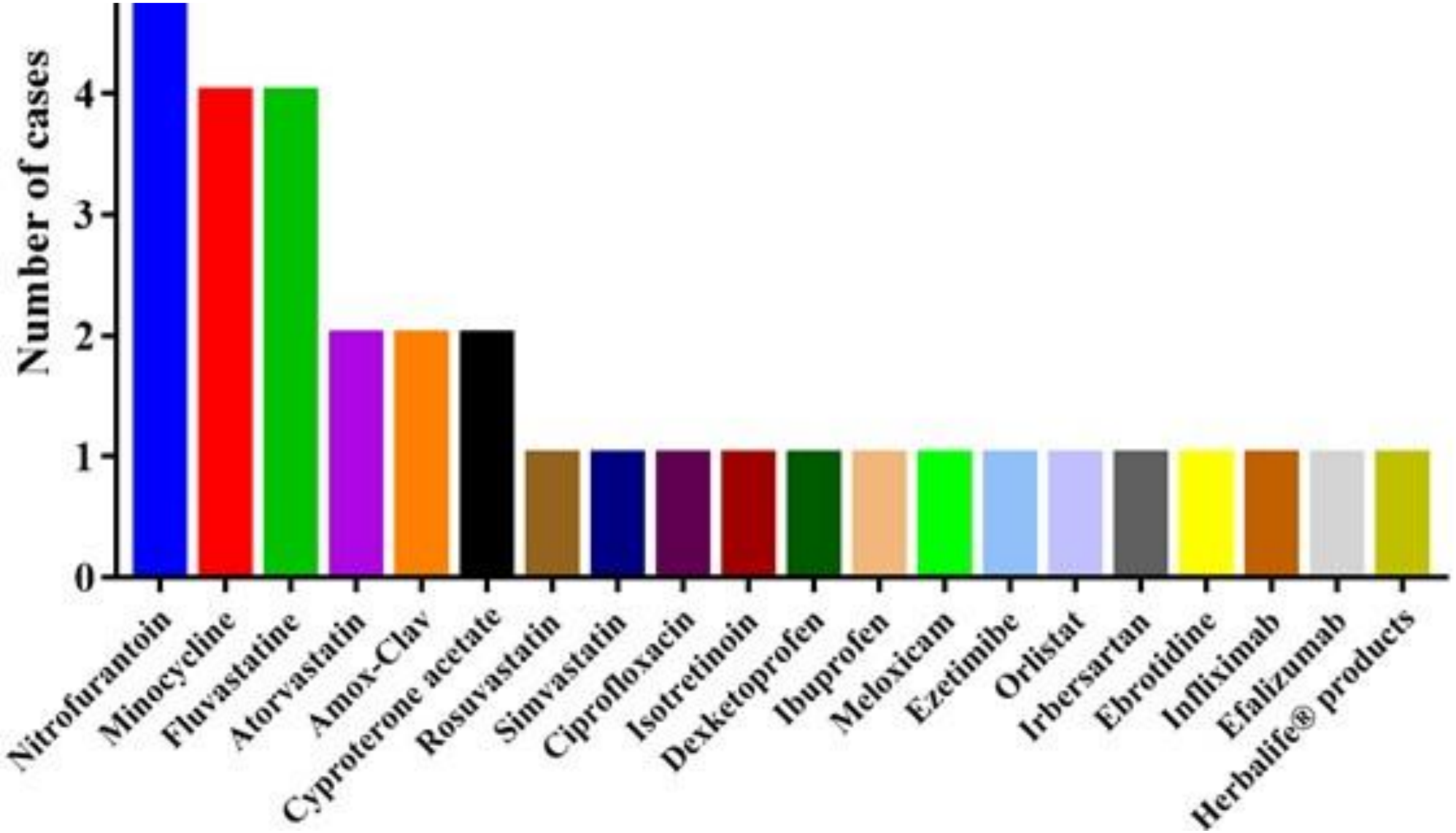
	No immunosuppression (IS) (n=13)†	IS from the onset and then withdrawn (n=10)	IS from the onset and maintained (n=10)	*p* value
Female sex, n (%)	732 (53)	19 (58)	53 (75)	**0.001**
Age (y), mean±SD (range)	52±18 (11-91)	53±20 (15-86)	53±15 (17-80)	0.971
Treatment duration (d), median (IQR)	214 (77-314)[b]	113 (41-748)[c]	28 (6-56)	**0.015**
Liver profile at DILI recognition (x ULN), median (IQR)				
Total bilirubin	1.5 (1.3-3.4)	4.4 (1.5-7.0)	3.2 (2.3-9.5)	0.303
Alanine aminotransferase (ALT)	13 (9.4-19)	28 (15-44)	29 (21-34)	0.079
Severity, n (%)				**0.047**
Mild	9 (69)	3 (30)	2 (20)	
Moderate	3 (23)	6 (60)	5 (50)	
Severe/Fatal/liver transplantation	1 (7.7)	1 (10)	3 (30)	
Relapse, n (%)	3 (25)	4 (40)	2 (20)	0.491

† A patient who received ursodeoxycholic acid and another patient who was treated with immunosuppressants only after relapsing were classified in this group.

[b] Significant differences between first and third column. [c] Significant differences between second and third column ($p<0.05$).

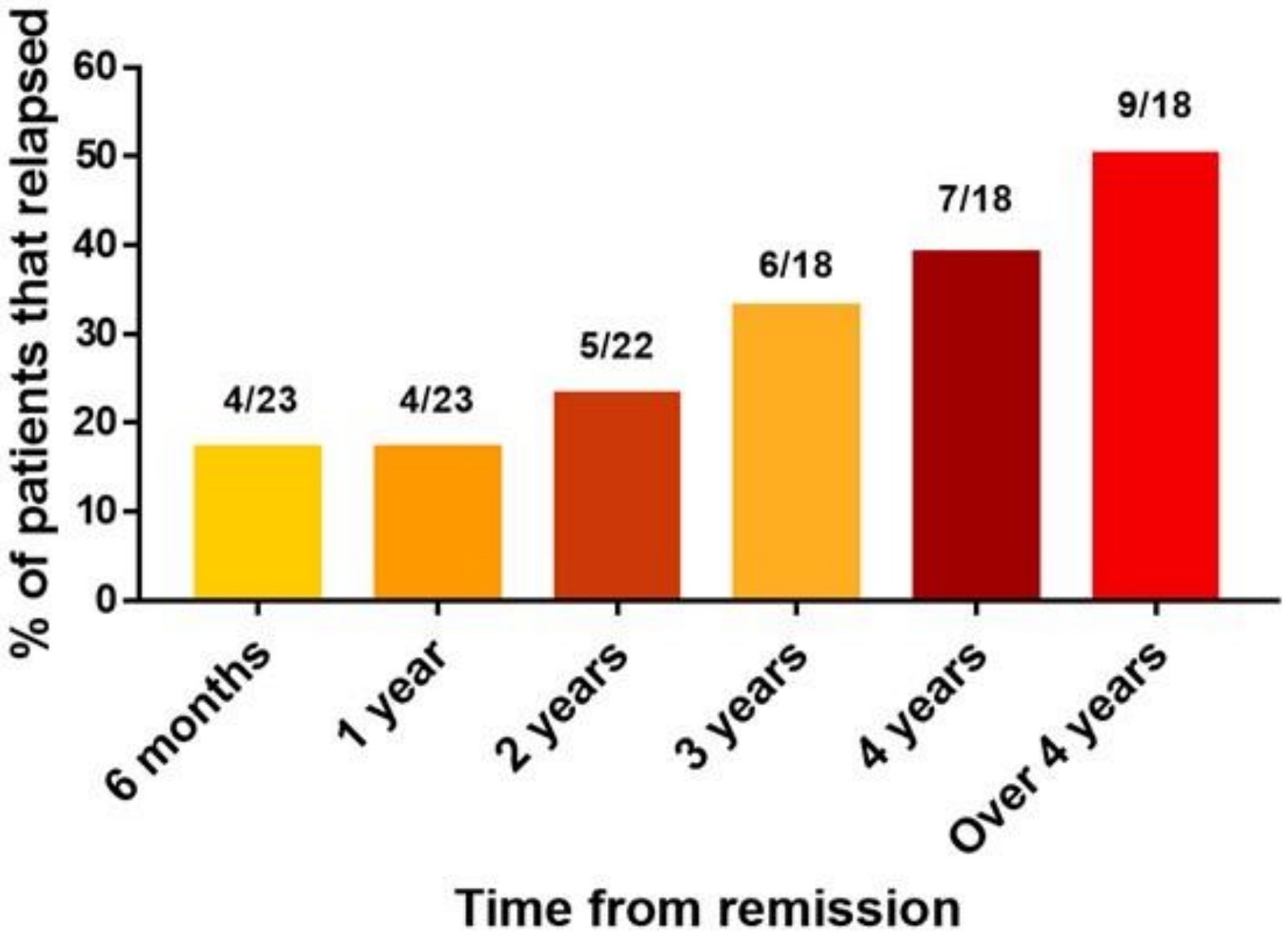
García-Cortés, Ortega-Alonso, Matilla-Cabello *et al*. *Liver Int*. 2023

Most frequent culprit drugs in drug-induced autoimmune-like hepatitis cases in the Spanish and the LATINDILI Registries



García-Cortés, Ortega-Alonso, Matilla-Cabello *et al*. *Liver Int*. 2023

Cumulative relapse rate of drug-induced autoimmune-like hepatitis cases



García-Cortés, Ortega-Alonso, Matilla-Cabello *et al*. *Liver Int*. 2023

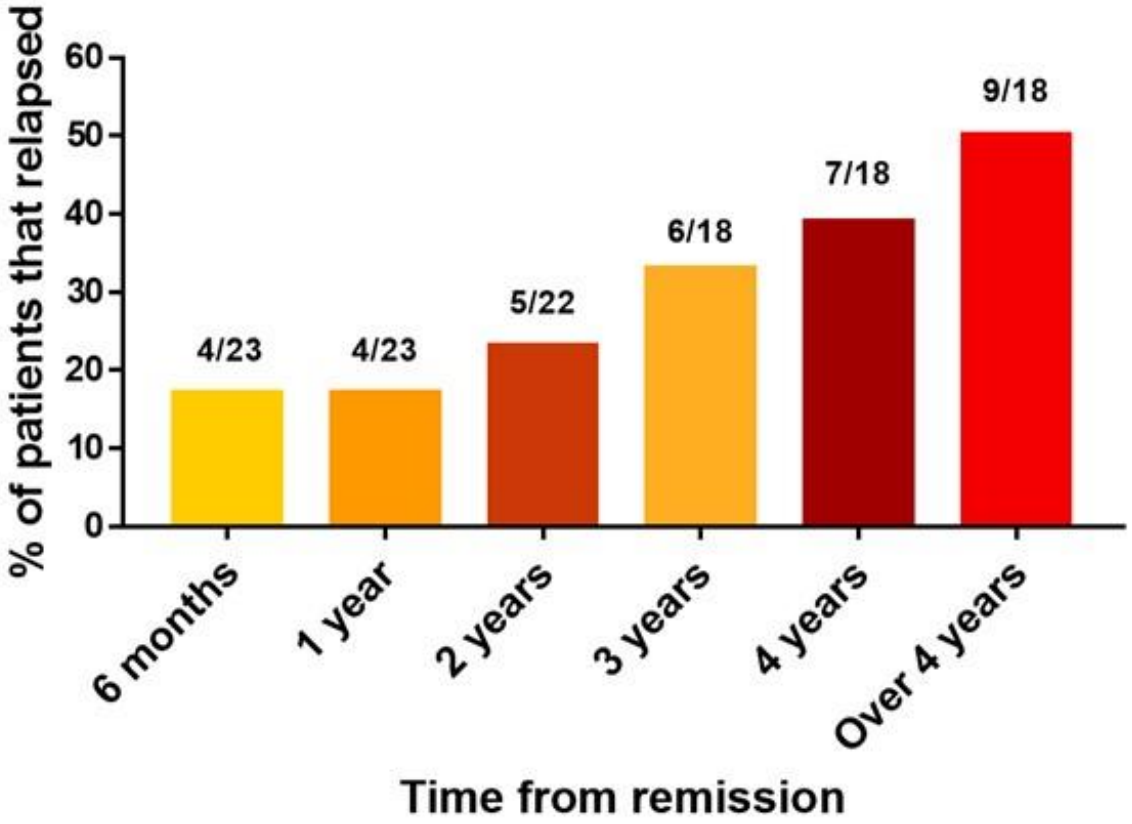
Characteristics of DILI cases with autoimmune features that did and did not relapse

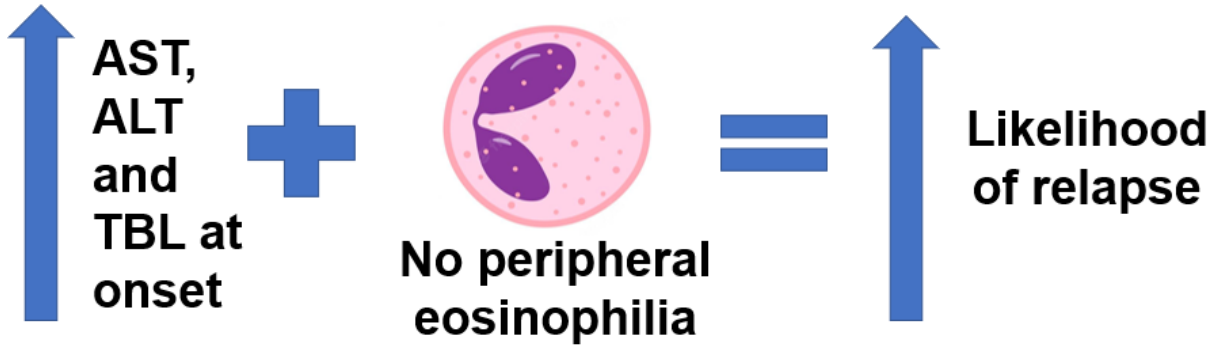
	No relapse† (n=14)	Relapse (n=9)	*p* value
Female sex, n (%)	7 (50)	8 (89)	0.086
Age (y), mean ± SD (range)	59±22 (16-86)	49±15 (15-67)	0.294
Eosinophilia, n (%)	6 (43)	0 (0)	**0.048**
Treatment duration (d), median (IQR)	205 (102-314)	77 (10-748)	0.186
Liver profile at DILI recognition (x ULN), median (IQR)			
Total bilirubin	1.5 (1.1-3.0)	7 (3.6-9.5)	**0.008**
Aspartate aminotransferase (AST)	13 (10-19)	29 (18-36)	**0.029**
Alanine aminotransferase (ALT)	12 (10-19)	31 (28-40)	**0.038**
Normalization time (d), median (IQR)	100 (90-202)	202 (176-395)	**0.025**

† Patients who did not receive immunosuppressive treatment, or it was withdrawn before an eventual relapse. The patient who underwent liver transplantation was excluded from this analysis.

García-Cortés, Ortega-Alonso, Matilla-Cabello *et al*. *Liver Int*. 2023

Relapse rate of DILI with autoimmune features cases over time after remission



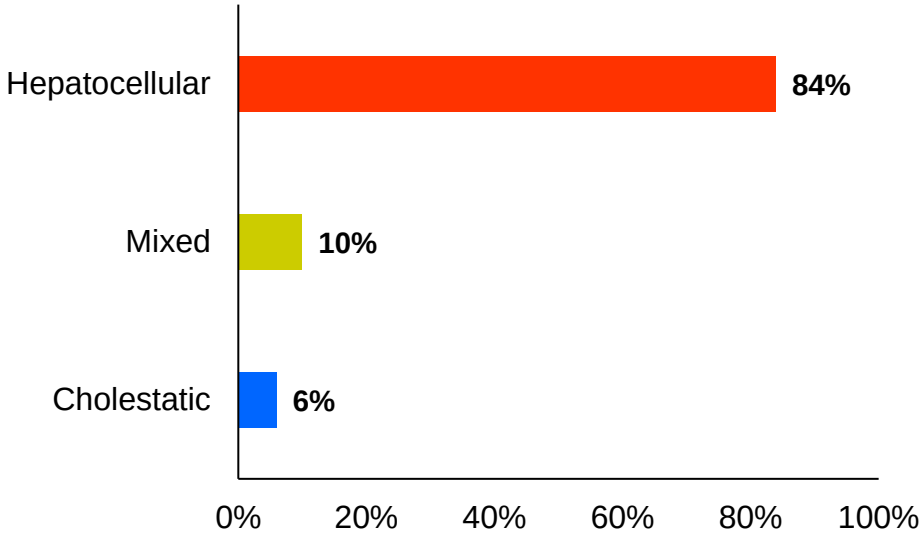


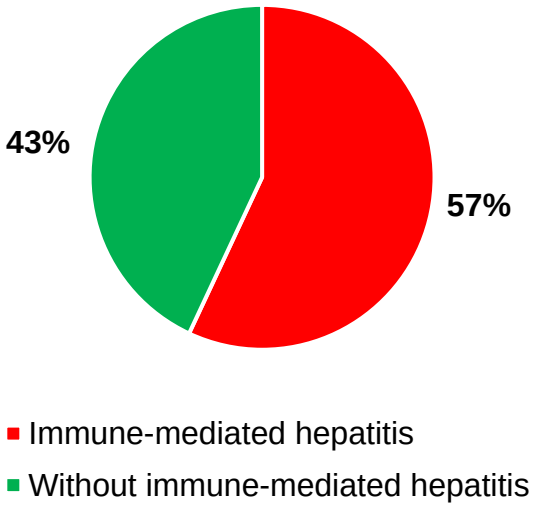
Analysis performed with the chi-square test with Fisher's correction and Mann-Whitney U test.

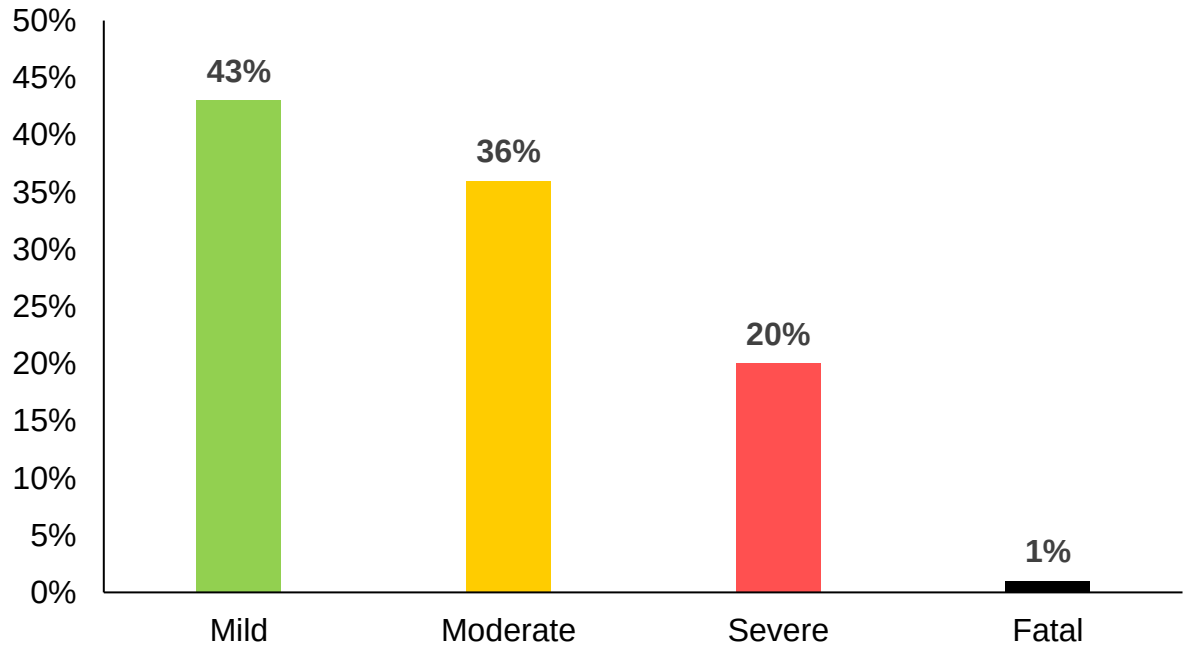
The cumulative prevalence of relapse was calculated considering the number of patients with available follow-up information at each time segment.

García-Cortés, Ortega-Alonso, Matilla-Cabello *et al*. *Liver Int*. 2023

DILI after SARS-CoV- 2 vaccination





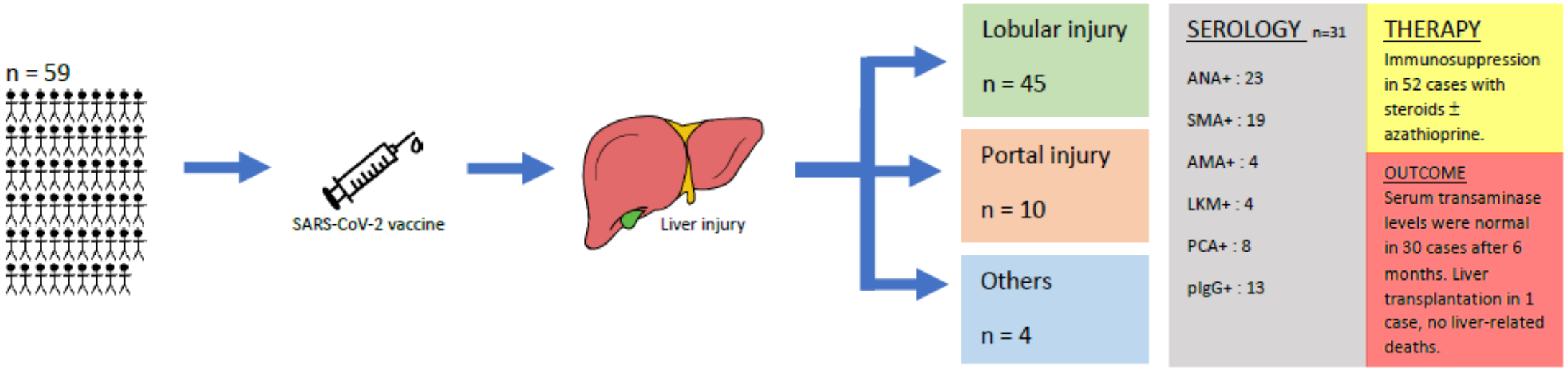


Efe et al., *Hepatology.* 2022 May 14:10.1002/hep.32572. doi: 10.1002/hep.32572. 2022

Research article JHEP|Reports

Histological and serological features of acute liver injury after SARS-CoV-2 vaccination

Greta Codoni,[1,†] Theresa Kirchner,[2,7,†] Bastian Engel,[2,7] Alejandra Maria Villamil,[3] Cumali Efe,[4] Albert Friedrich Stättermayer,[5] Jan Philipp Weltzsch,[6,7] Marcial Sebode,[6,7] Christine Bernsmeier,[8] Ana Lleo,[9,31] Tom JG. Gevers,[7,10] Limas Kupčinskas,[7,11] Agustin Castiella,[12] Jose Pinazo,[13] Eleonora De Martin,[14] Ingrid Bobis,[15] Thomas Damgaard Sandahl,[16] Federica Pedica,[17] Federica Invernizzi,[17] Paolo Del Poggio,[18] Tony Bruns,[7,19] Mirjam Kolev,[20] Nasser Semmo,[20] Fernando Bessone,[21] Baptiste Giguet,[22] Guido Poggi,[23] Masayuki Ueno,[24,32] Helena Jang,[25] Gülsüm Özlem Elpek,[26] Neşe Karadağ Soylu,[27] Andreas Cerny,[28] Heiner Wedemeyer,[2,7] Diego Vergani,[29] Giorgina Mieli-Vergani,[29] M. Isabel Lucena,[13,30] Raul J. Andrade,[13,30] Yoh Zen,[29] Richard Taubert,[2,7,#] Benedetta Terziroli Beretta-Piccoli[1,28,29,#,*]

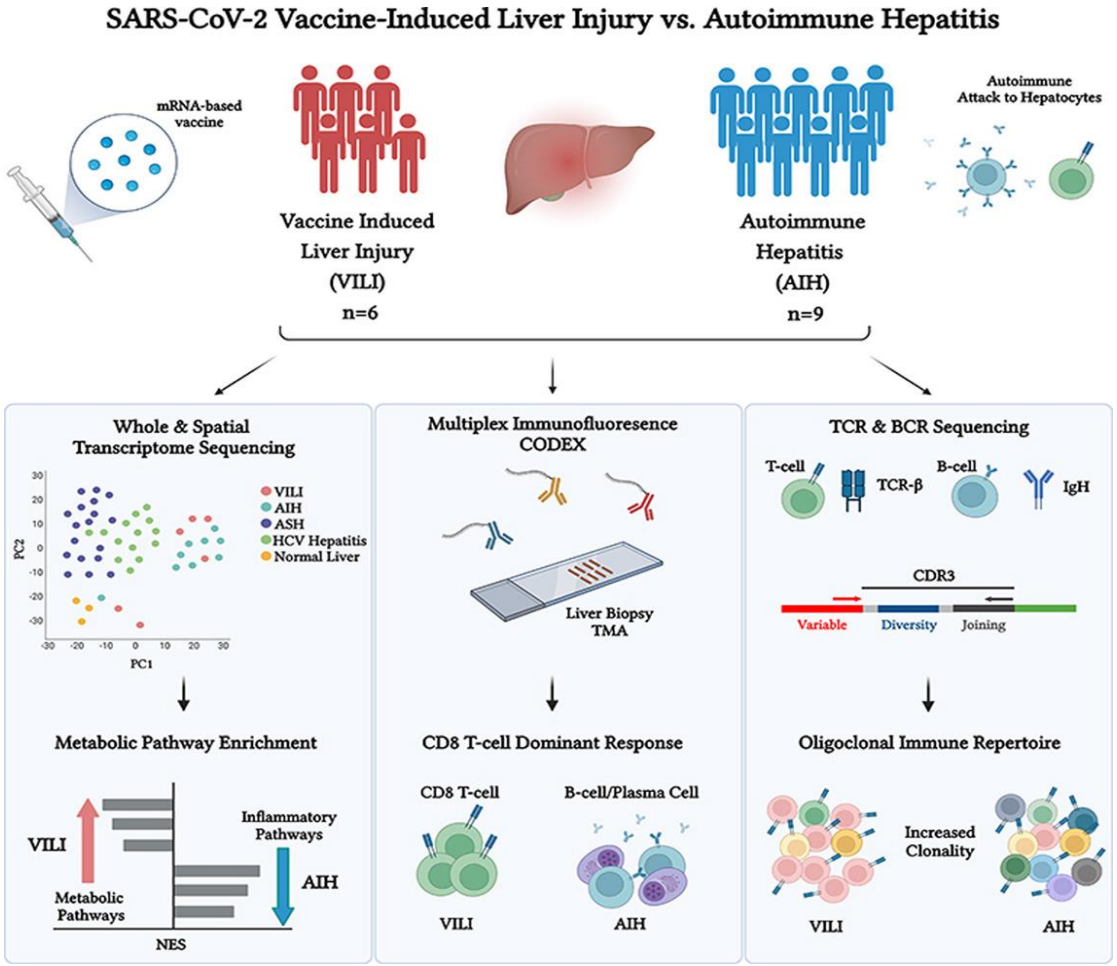


Codoni et al JHEP Rep. 2022; 13;5(1):100605. doi: 10.1016/j.jhepr.2022.100605. eCollection 2023 Jan.

Morphologic and molecular analysis of liver injury after SARS-CoV-2 vaccination reveals distinct characteristics

Journal of Hepatology DOI: 10.1016/j.jhep.2023.05.020

Sarp Uzun, Carl Zinner, Amke C. Beenen, Ilaria Alborelli, Ewelina M. Bartoszek, Jason Yeung, Byron Calgua, Matthias Reinscheid, Peter Bonsert, Anna K. Stalder, Jasmine Haslbauer, Jürg Vosbeck, Luca Mazzucchelli, Tobias Hoffmann, Luigi M. Terracciano, Gregor Hutter, Michael Manz, Isabelle Panne, Tobias Böttler, Maike Hofmann, Bertram Bengsch, Markus H. Heim, Christine Bernsmeier, Sizun Jiang, Alexandar Tzankov, Benedetta Terziroli Beretta-Piccoli, Matthias S. Matter



PRO-EURO DILI NETWORK

Prospective European Drug-induced Liver Injury Network

IAIHG

INTERNATIONAL AUTOIMMUNE HEPATITIS GROUP

cost

EUROPEAN COOPERATION IN SCIENCE AND TECHNOLOGY

COST is supported by the EU Framework Programme Horizon 2020

Consensus conference on Drug-Induced Autoinmune Hepatitis (DI-AIH).

Parador de Nerja, Málaga (Spain).

02-03 March 2022

***Scientific Programme Committee*:** *RJ Andrade, GP Aithal, Einar S Björnsson, MI Lucena, G Mieli-Vergani, D Vergani, R Liberal, YS de Boer.*

AIMS: To to establish a consensus for standardized nomenclature in DI-ALH, best practices in management and identify key gaps in the diagnostic and mechanistic biomarkers

Seminar

JOURNAL
OF HEPATOLOGY

Nomenclature, diagnosis and management of drug-induced autoimmune-like hepatitis (DI-ALH): An expert opinion meeting report

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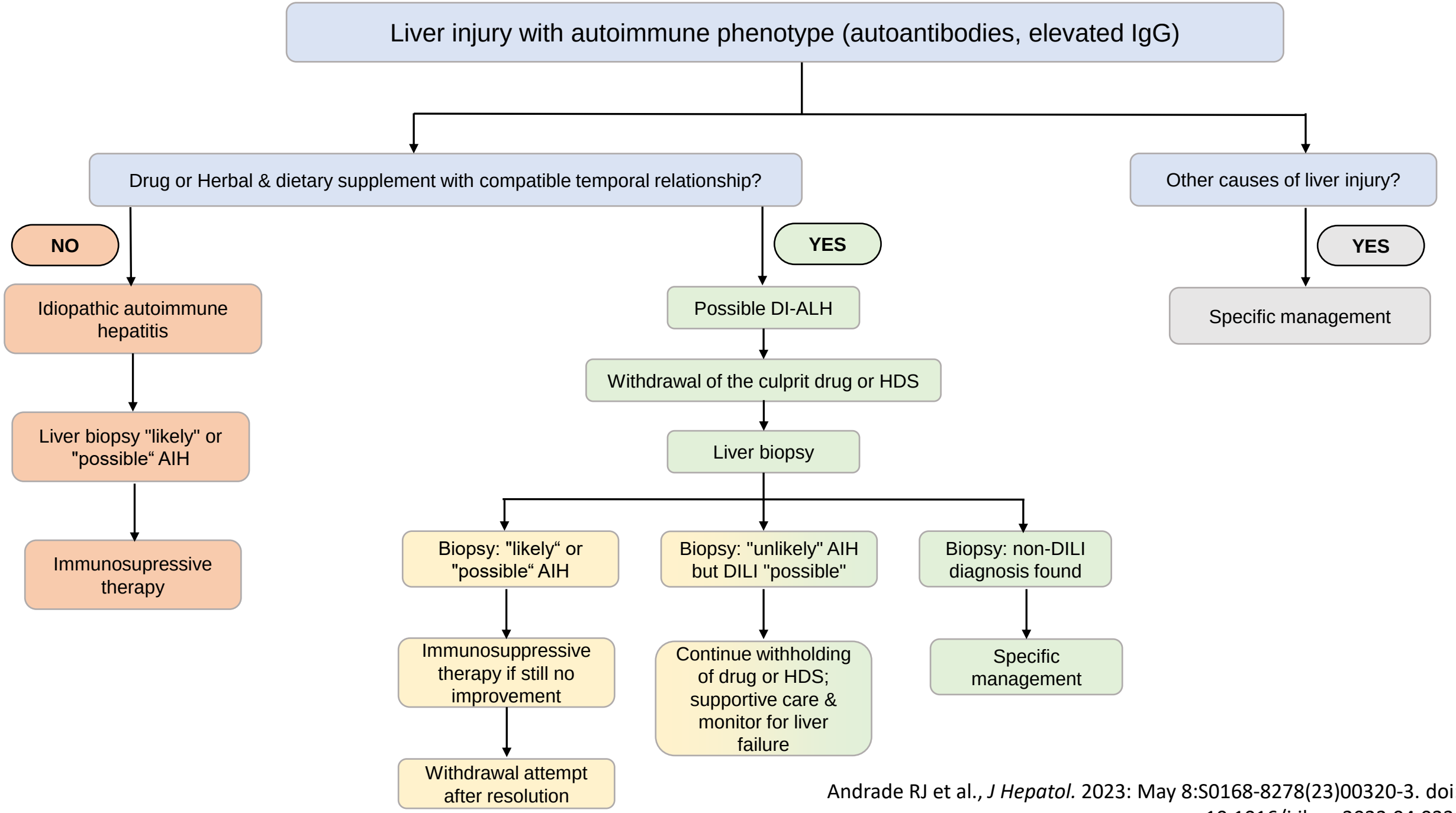
Summary

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 summarises the major topics discussed at a joint International Conference held between the 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 the condition often resolves spontaneously after withdrawal of the implicated drug, whereas patients with AIH mostly require 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



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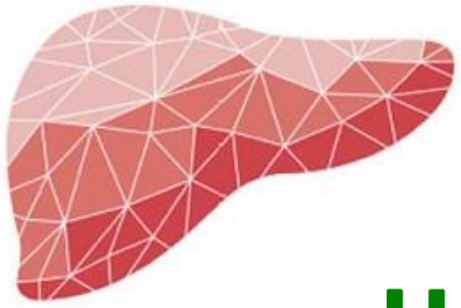

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