Epidemiology of drug and herbal induced liver injury: the evolving profile

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University of Iceland
Established in 1911

Drug-induced liver injury

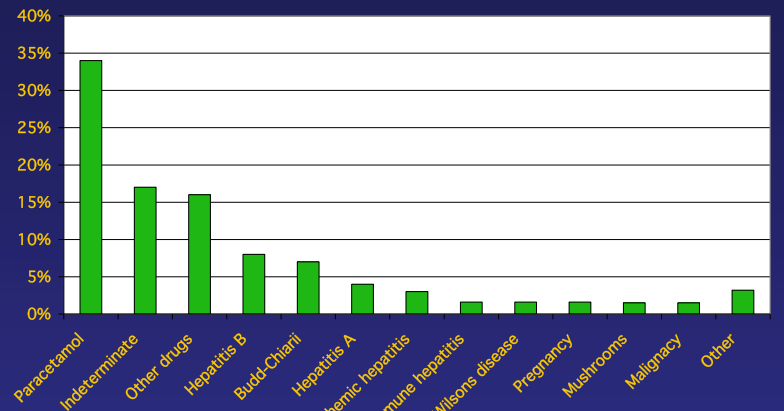
- DILI is one of most common reasons for termination of drug development of otherwise promising drugs
- DILI has become the major single cause of withdrawal of drugs from the market
- Is the most common cause of acute liver failure in the US, UK, Germany and Sweden

HOW COMMON IS DRUG-INDUCED LIVER DISEASE?

- Among patients with acute liver failure?
- In jaundiced patients?
- In patients referred to a gastroenterologist/hepatologist for evaluation of liver disease?
- In the general population?

Causes of acute liver failure in Sweden and USA

- The most common cause is DILI
- Most commonly paracetamol-intentional and unintentional intoxication
- Other drugs: 15-17%



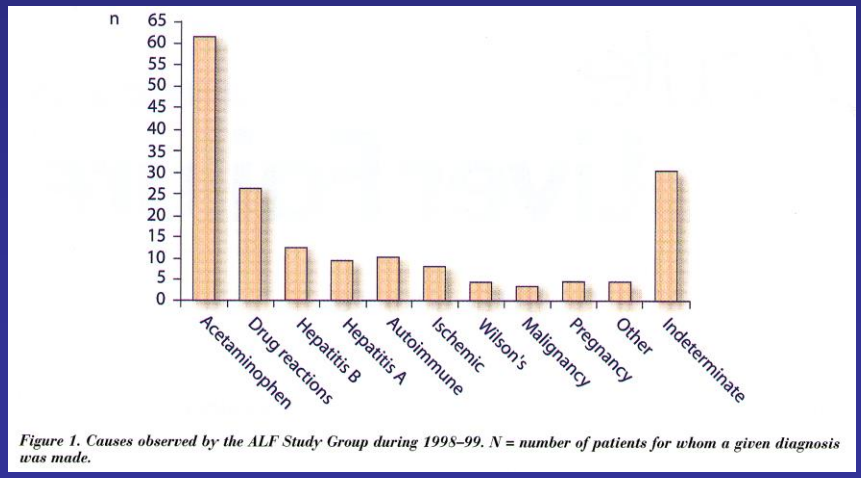
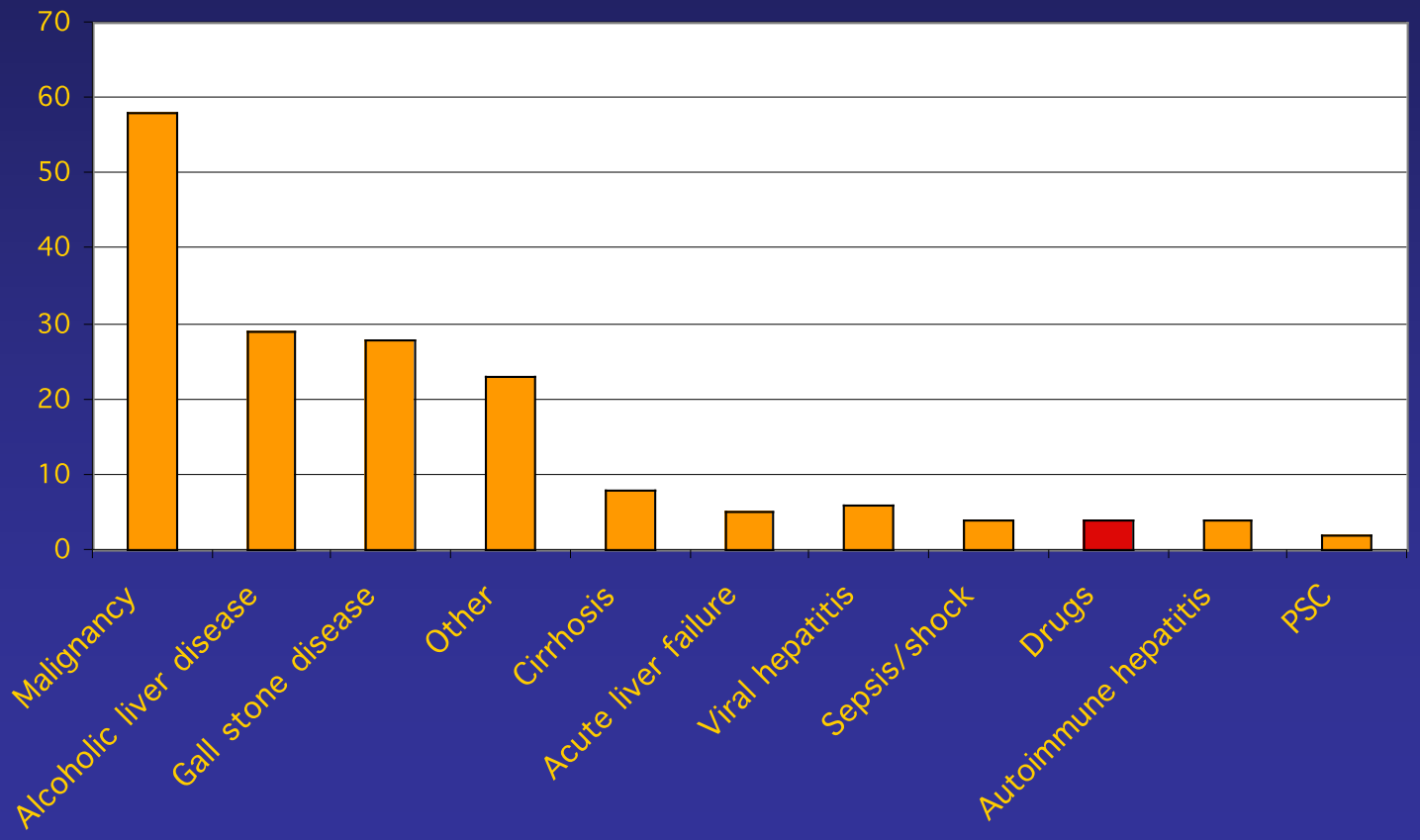


Figure 1. Causes observed by the ALF Study Group during 1998–99. N = number of patients for whom a given diagnosis was made.

Causes of jaundice in 171 patients Sweden 2002-due to drugs in 5% of cases (Björnsson et al. Scand J Gastenterol 2003; 38: 86-94)



DILI in the outpatient hepatology clinic in Sweden

(Benito de Valle et al Aliment Pharmacol & Therapeutics 2006)

- All cases in the outpatient clinic with a diagnosis of a liver disease 1994-2005 at Sahlgrenska University hospital were reviewed (1164 cases)

- Causality assessment was based on the International Consensus Criteria

DILI in the outpatient hepatology clinic

- DILI constituted 6% of all out-patients
- DILI constituted 3% of all referrals wheras 3% was followed-up after hospitalization for DILI

GP database UK
(de Abajo.et al Br J Clin Pharm 2004)

- A total of 1.636.792 person followed 1994-1999 in general practice database in UK
- DILI cases identified by computer search-files reviewed manually
- ALT (ALP and bilirubin) ≥ x 2 ULN
- 128 DILI cases suspected

GP database UK

- The strongest associations seen with:
  - Chlorpromazine
  - Amoxicillin/clavulanic acid
  - Flucloxacillin
  - Macrolides
  - Tetracyclines
- The highest crude incidence rates for:
  - Chlorpromazine
  - Azathioprine
  - Sulphasalazine

The true Incidence of DILI in the general population?

- Sgro et al. Hepatology 2002; 38: 531-2
- Prospective study of all new cases of DILI in Nevers (81 000 inhabitants) France 1997-2000
- 34 cases of DILI (82% outpatients), recovery for 32, 2 died

Sgro et al. Hepatology 2002

- Incidence 14 per 100 000 and year
- Corresponds to 8.000 cases per year in France and 500 deaths!
- **Number of DILI was 16 x the spontaneous reporting to the french authorities**

Bjornsson et al. Incidence, Presentation and Outcomes in Patients with Drug-Induced Liver Injury in the General Population of Iceland Gastroenterology 2013; 32: 3-13.

- Little is known of the incidence of DILI in population cohorts, in France: 14 per 100, 000
- Very little information available for patients at risk, highest crude incidence rates 1 per 1000 for chlorpromazine, azathioprine and sulphasalazine (de Abajo et al. Brit J Clin Pharmacol 2004)

Bjornsson et al. Incidence, Presentation and Outcomes in Patients with Drug-Induced Liver Injury in the General Population of Iceland in Iceland Gastroenterology 2013; 32: 3-13.

- 96 cases in 2 years: Crude incidence 19 cases per 100, 000 inhabitants
- Single prescription agent in 75%, dietary supplements 16%, multiple drugs in 9%. Jaundice (27%), 23% hospitalized. 17% developed in hospital
- Most common drugs: Amoxicillin-Clavulanate (22%), diclofenac (6%), azathioprine (4%), infliximab (4%), nitrofurantoin (4%)

The most common drugs and risk of DILI- Outpatients

Drug	Number of patients	Number of DILI	Proportion 1/
Amoxicillin/clavulanate	35,252	15	2350
Diclofenac	55689	6	9480
Azathioprine	541	4	133
Infliximab	593	4	148
Nitrofurantoin	5709	4	1427
Isotretinoin	2488	3	829
Atorvastatin	7390	2	3695
Doxycycline	33619	2	16810

Hospitalized patients

Amoxicillin/clavulanate	4340	6	723

Conclusions

- The incidence of DILI was the highest reported to date
- Amoxicillin-clavulanate was the most commonly implicated agent, higher among hospitalized than outpatients
- The highest risk of hepatotoxicity was associated with azathioprine and infliximab

How common is herbal associated hepatotoxicity?

- Herbal associated hepatotoxicity has not been systematically studied

- 5% of cases were due to herbs in Sweden (De valle et al. 2006) and 6% in the Spanish hepatotoxicity registry(1994-2018, Stephens et al. J Hepatology 2021)

How common is herbal associated hepatotoxicity?

- Among patients undergoing liver transplantation for acute liver failure due to DILI, 5% were considered to be due to herbs (Russo et al. Liver Transpl 2004)

How common is herbal associated hepatotoxicity?

- Among patients undergoing liver transplantation for acute liver failure due to DILI, 5% were considered to be due to herbs (Russo et al. Liver Transpl 2004)
- In the Drug-induced liver injury networkprospective study (16%) had herbal and/or dietary supplements as the presumptive cause (Chalasani Gastroenterology 2015)
-

How common is herbal associated hepatotoxicity?

Pro-Euro-DILI (2016–2021) (*n* = 246)	Spanish DILI Registry (1994–2018) (*n* = 843)	DILIN (2004–2013) (*n* = 899)	Indian Network of DILI (2013–2018) (*n* = 1288)	Icelandic study (2010–2011) (*n* = 96)
Amoxicillin-clavulanate (12%)	Amoxicillin-clavulanate (22.9%)	Amoxicillin-clavulanate (10.1%)	Anti-TBC drugs (46.4%)	Amoxicillin-clavulanate (22%)
Flucloxacillin (11%)	Anti-TBC drugs (4.5%)	Isoniazid (5.3%)	Antiepileptics (8.1%)	Diclofenac (6.3%)
Atorvastatin (8.0%)	Ibuprofen (3.0%)	Nitrofurantoin (4.7%)	Non anti-TBC drugs (6.5%)	Nitrofurantoin (4.2%)
Nivolumab and ipilimumab (8.0%)	Isoniazid (2.5%)	Sulfamethoxazole-trimethoprim (3.4%)	Antimetabolites (3.8%)	Azathioprine (4.2%)
Infliximab (5.0%)	Atorvastatin (1.9%)	Minocycline (3.1%)	Anti-retroviral (3.5%)	Infliximab (4.2%)
Nitrofurantoin (4.5%)	Diclofenac (1.8%)	Cefazolin (2.2%)	NSAIDs (2.6%)	Isotretinoin (3.1%)
Disulfiram (2.0%)	Ticlopidine (1.4%)	Azithromycin (2.0%)	Hormones (2.5%)	Atorvastatin (2.1%)
Ibuprofen (2.0%)	Azathioprine (1.3%)	Ciprofloxacin (1.8%)	Statins (1.4%)	Doxycycline (2.1%)
Azathioprine, diclofenac, isoniazid, metamizole sodium, methotrexate, methyldopa, methylepitiostanol, ribociclib, anti-TBC drugs, terbinafine (1.5%)	Fluvastatin (1.3%) Simvastatin (1.3%) Paroxetine (1.2%) Nimesulide (1.1%)	Levofloxacin (1.4%) Diclofenac (1.3%) Phenytoin (1.3%) Methyldopa (1.2%)	Others (11.3%)	Imatinib (1%) Isoniazid (1%) Cefalexin (1%) Phenytoin (1%)
HDS and AAS (6.0%)	HDS and AAS (6.0%)	HDS (16.1%)	CAM (13.9%)	HDS (16%)

Evolving Profile-relatively new DILI culprits

- TFN-alpha inhibitors
- Check point inhibitors
- Green-tea extract
- DI-ALH=Drug-induced Autoimmune like hepatitis
- Covid vaccines
- Tinospora cordifola

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Drug-Induced Liver Injury — Types and Phenotypes

Jay H. Hoofnagle, M.D., and Einar S. Björnsson, M.D.

Table 1. Drug-Induced Liver Injury According to Type.*

Variable	Direct Hepatotoxicity	Idiosyncratic Hepatotoxicity	Indirect Hepatotoxicity
Frequency	Common	Rare	Intermediate
Dose-related	Yes	No	No
Predictable	Yes	No	Partially
Reproducible in animal models	Yes	No	Not usually
Latency (time to onset)	Typically rapid (days)	Variable (days to years)	Delayed (months)
Phenotypes	Acute hepatic necrosis, serum enzyme elevations, sinusoidal obstruction, acute fatty liver, nodular regeneration	Acute hepatocellular hepatitis, mixed or cholestatic hepatitis, bland cholestasis, chronic hepatitis	Acute hepatitis, immune-mediated hepatitis, fatty liver, chronic hepatitis
Most commonly implicated agents	High doses of acetaminophen, niacin, aspirin, cocaine, IV amiodarone, IV methotrexate, cancer chemotherapy	Amoxicillin–clavulanate, cephalosporins, isoniazid, nitrofurantoin, minocycline, fluoroquinolones, macrolide antibiotics	Antineoplastic agents, glucocorticoids, monoclonal antibodies (against tumor necrosis factor, CD20, checkpoint proteins), protein kinase inhibitors
Cause	Intrinsic hepatotoxicity when agent given in high doses	Idiosyncratic metabolic or immunologic reaction	Indirect action of agent on liver or immune system

GASTROENTEROLOGY 2013;144:1419–1425

CLINICAL—LIVER

Incidence, Presentation, and Outcomes in Patients With Drug-Induced Liver Injury in the General Population of Iceland

EINAR S. BJÖRNSSON,[1,2] OTTAR M. BERGMANN,[1] HELGI K. BJÖRNSSON,[2] RUNAR B. KVARAN,[2] and SIGURDUR OLAFSSON[1]

[1]Department of Internal Medicine, Section of Gastroenterology and Hepatology, National University Hospital, Reykjavik; and [2]Faculty of Medicine, University of Iceland, Iceland

- 96 cases in 2 years: Crude incidence 19 cases per 100, 000 inhabitants
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TNF-alpha inhibitors-induced DILI

J Hepatol. 2021 Sep 3;S0168-8278(21)02022-5. doi: 10.1016/j.jhep.2021.08.024.
Online ahead of print.

Infliximab-induced liver injury: Clinical phenotypes, autoimmunity and the role of corticosteroid treatment

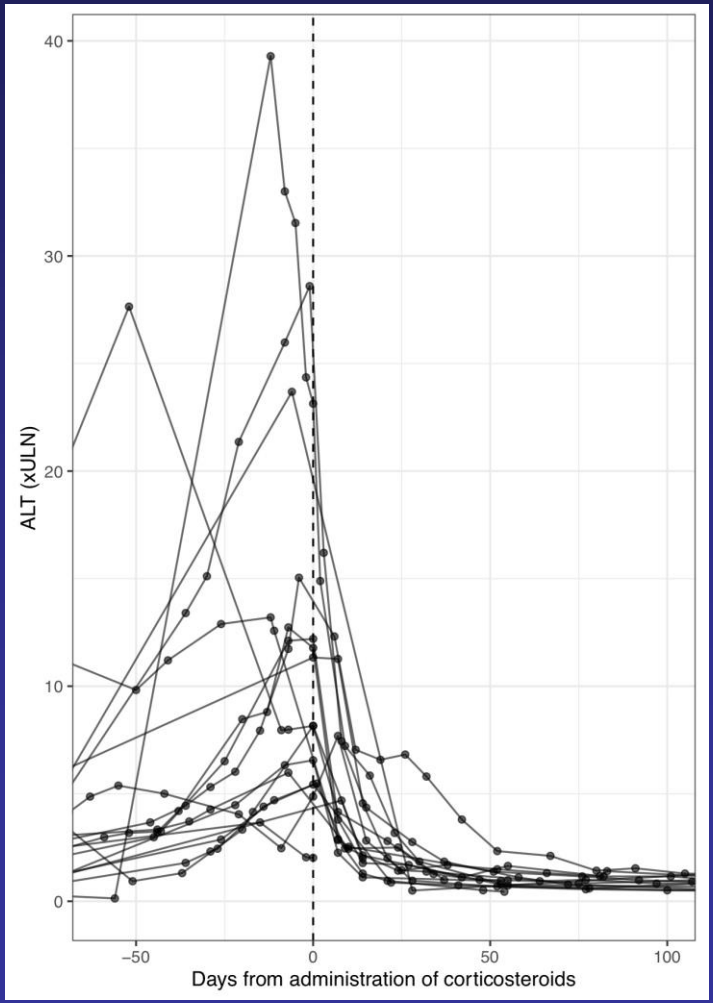
Helgi Kristinn Björnsson [1], Bjorn Gudbjornsson [2], Einar Stefan Björnsson [3]

Infliximab-induced DILI

Bjornsson et al. J Hepatology 2021

- Corticosteroid treatment was initiated in 17 patients (47%) and one patient was concomitantly treated with azathioprine. Median dose 30 mg
- The median duration of corticosteroids was 84 days
- Median time from onset of liver injury to corticosteroid treatment initiation was 44 days (IQR 14-69, range 0-88).

The progression of ALT elevations in all patients treated with corticosteroids



Outcomes

- **Corticosteroid treatment was tapered in all patients**
  - **No patient had a relapse with an elevation in liver enzymes**
- **75% patients were switched to another biologic treatment**
  - **No cases of DILI caused by a second biologic treatment**

Drug-induced AIH-like hepatitis (DI-ALH)

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]

Drug-induced AIH-like hepatitis (DI-ALH)

- Minocycline, nitrofurantoin, methyldopa, and infliximab well recognized
- In the recent paper most commonly reported agents of DI-AILH were interferons (*n* = 37), statins (*n* = 24), methylpredni-solone (MPS) (*n* = 16), adalimumab (*n* = 10), imatinib (*n* = 8), and diclofenac (*n* = 7). Tinospora cordifolia and Khat were the only HDS with probable DI- AILH cases.

Liver injury due to check point inhibitors

- In a study of 17 melanoma patients with DILI due to CPI, other concomitant immune-mediated adverse effects were observed in 47% (gastrointestinal, dermatological, endocrine, lung disorders): Huffman et al. 2018
- Among 100 DILI patients (53% melanom), 45% had concomitant immune-mediated adverse effects, dermatological (14%) and colitis (9%) most common: Miller et al. 2019
- Rarely ALF has been the initial presentation

Check point inhibitors: Management of DILI

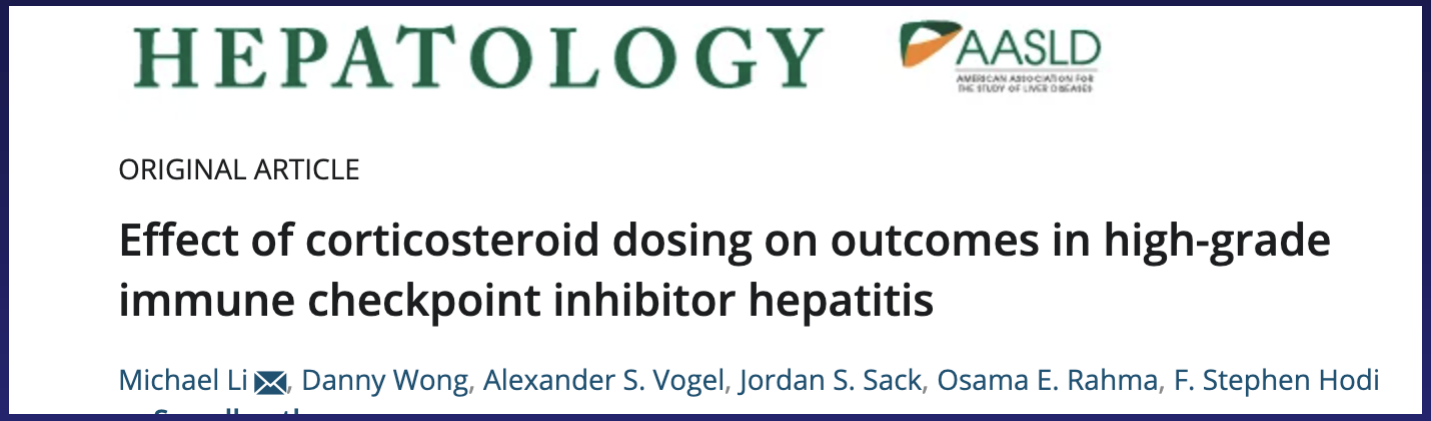
- Doubtful if a liver biopsy will change management
- In a patient with a recent hepatocellular jaundice in a patient with no liver metastases, with no resolution of ALT after drug discontinuation within days with Grade III-IV, corticosteroids are usually but NOT ALWAYS needed

Published in final edited form as:
Mod Pathol. 2021 February ; 34(2): 426–437. doi:10.1038/s41379-020-00653-1.

Immune checkpoint inhibitor related liver injury: Histopathologic pattern does not correlate with response to immune suppression

Justine V. Cohen[*], **Michael Dougan**[**,****], **Leyre Zubiri**[***,****], **Kerry L. Reynolds**[***,****], **Ryan J. Sullivan**[***,****], **Joseph Misdraji**[+,****]

- In conclusion, we found that a liver biopsy in patients on immune checkpoint inhibitors might not predict the need for steroids, the length of time that steroids is required, or the need for secondary immunosuppression”



- In a recent study, it was demonstrated that initial treatment with 1 mg/kg/day provided similar liver tests improvement as doses >1.5 mg/kg/day, which was also associated with a reduced risk of steroid-induced adverse effects in comparison with higher-dose regimens

SARS-CoV-2 vaccine

- AIH-like picture related to SARS-CoV-2 vaccine has been reported.
- Several case reports and case series with an autoimmune phenotype observed with all COVID-19 vaccines

- Efe et al. Liver injury after SARS-CoV-2 vaccination: Features of immune-mediated hepatitis, role of corticosteroid therapy and outcome. Hepatology. 2022;76(6):1576-86.
- Codoni Get al. Histological and serological features of acute liver injury after SARS-CoV-2 vaccination. JHEP Rep. 2023;5(1):100605

Tinospora cordifola

- Several herbals have characteristic features of drug-induced autoimmune like hepatitis. Nagral and colleagues showed features of DIALH in 4 of their six patients with Giloy (TC)
- Kulkarni and colleagues showed autoimmune features in 55% of their 43 patients with DILI that included both immunological and histological features

NagralA, et al. Herbal Immune booster-induced liver injury in the COVID-19 pandemic - a case series. J Clin Exp Hepatol. 2021 Jul 2

Kulkarni A et al. Hepatol Comm 2022;6:1289-1300

Green tea extract induced liver injury

- Has turned out to be the best documented herbal and dietary supplement (HDS) induced liver injury
- Included in many different HDS such as Herbalife ® , SLIMQUICK® Hydroxycut ® etc.

Published in final edited form as:

Hepatology. 2021 June ; 73(6): 2484–2493. doi:10.1002/hep.31538.

HLA-B*35:01 and Green Tea Induced Liver Injury

Jay H. Hoofnagle, M.D., Herbert L. Bonkovsky, M.D., Elizabeth J. Phillips, M.D., Yi-Ju Li, Ph.D., Jawad Ahmad, M.D., Huiman Barnhart, Ph.D., Francisco Durazo, M.D., Robert J. Fontana, M.D., Jiezhun Gu, Ph.D., Ikhlas Khan, Ph.D., David E. Kleiner, M.D., Ph.D., Christopher Koh, M.D., Don C. Rockey, M.D., Leonard B. Seeff, M.D., Jose Serrano, M.D., Ph.D., Andrew Stolz, M.D., Hans L. Tillmann, M.D., Raj Vuppalanchi, M.D., Victor J. Navarro, M.D., Drug-Induced Liver Injury Network.

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HLA-B*35:01 and Green Tea Induced Liver Injury

Jay H. Hoofnagle, M.D., Herbert L. Bonkovsky, M.D., Elizabeth J. Phillips, M.D., Yi-Ju Li, Ph.D., Jawad Ahmad, M.D., Huiman Barnhart, Ph.D., Francisco Durazo, M.D., Robert J. Fontana, M.D., Jiezhun Gu, Ph.D., Ikhlas Khan, Ph.D., David E. Kleiner, M.D., Ph.D., Christopher Koh, M.D., Don C. Rockey, M.D., Leonard B. Seeff, M.D., Jose Serrano, M.D., Ph.D., Andrew Stolz, M.D., Hans L. Tillmann, M.D., Raj Vuppalanchi, M.D., Victor J. Navarro, M.D., Drug-Induced Liver Injury Network.

- Among 1414 patients enrolled in the U.S. Drug Induced Liver Injury Network who underwent formal causality assessment, 40 cases (3%) were attributed to green tea, 202 to dietary supplements without green tea, and 1142 to conventional drugs. The clinical features of green tea cases and representation of HLA class I and II alleles in cases and controls were analyzed in detail

Results

- Patients with green tea-associated liver injury ranged in age from 17 to 69 years (median = 40) and developed symptoms 15 to 448 days (median = 72) after starting the implicated agent. The liver injury was typically hepatocellular (95%) with marked serum aminotransferase elevations and only modest increases in alkaline phosphatase. Most patients were jaundiced (83%)

Results

- The course was severe in 14 patients (35%), necessitating liver transplantation in 3 (8%),
- In three instances, injury recurred upon re-exposure to green tea with similar clinical features but shorter time to onset.
- HLA typing revealed a high prevalence of HLA-B*35:01, found in 72% of green tea cases but only 15% caused by other supplements and 12% attributed to drugs, the latter rate being similar to population controls 11%: 10.5% to 11.5%).

Conclusion

- Green tea-related liver injury has distinctive clinical features and close association with HLA-B*35:01 suggesting that it is idiosyncratic and immune-mediated.

Hepatotoxicity due to Hydroxycut: A case series.

Fong et al. Am J Gastro 2010.

- 17 new cases
  - 8 cases at several medical centers
  - 9 of 24 FDA MedWatch cases with sufficient information
  - One died, 3 required liver transplantation
- Causality assessment, severity grading by DILIN guidelines
  - Definite = 8
  - Very likely = 5
  - Probable = 2
  - Possible = 2

Hydroxycut-next generation

- 44 year old Monozygotic twin
- Jaundice and hepatocellular injury

P/S-ALP	U/L	97	138 H	174 H	241 H		227 H
P/S-gamma GT	U/L	43	60	53	57		74
P/S-ASAT	U/L	45 H	381 H	803 H	1304 H		1492 H
P/S-ALAT	U/L	84 H	1077 H	1766 H	2635 H		2733 H
P/S-LD	U/L						511 H
P/S-Lípasi	U/L						38
P/S-Amýlasi	U/L						94
P/S-Bílirúbín	µmól/L	27 H	75 H	133 H	261 H		264 H

Newly identified causes of DILI

Agents (ref)	Median age, *y*	Female, %	Latency (range)	Clinical features	Outcome
Immune checkpoint inhibitors (n = 100) (ref 17)	60	39	59 d (8–454)	70% hepatocellular, some DI-AILH	Deaths mostly caused by malignancy
TNF-α inhibitors (n = 36) (ref 16)	46	78	110 d (94–144)	Hepatocellular, some DI-AILH and secondary sclerosing cholangitis	Favorable, but transplants reported
COVID vaccines (n = 87) (ref 22)	48	63	15 d (3–65)	84% hepatocellular	1 liver transplant
Anabolic steroids (n = 60) (ref 13, 14)	32	1.7	73 d	Severe and prolonged cholestasis	No deaths or transplants
Green tea extract (n = 40) (ref 9)	40	74	5–448 d	95% hepatocellular	8% liver transplant

Newly identified causes of DILI

Ashwaganda (n = 7) (ref 10)	39	43	2–12 wk	Cholestatic/hepatocellular jaundice	No deaths or transplants
Turmeric (n = 10) (ref 12)	56	80	4–24 wk	Hepatocellular jaundice	1 death
Tinospora cordifola (n = 43) (ref 20)	50	54	46 d	Autoimmune features	Fatality in CLD, liver transplants reported
Kratom (n = 11) (ref 24)	40	18	14 d (5–23)	Mixed or cholestatic injury with jaundice	No deaths or transplants

Thank you for your attention