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Abstract

Drug-induced liver injury (DILI) remains the most common cause of acute liver failure (ALF) in the western world. Excluding paractamol overdose, nearly all DILI encountered in the clinical setting is idiosyncratic in nature, since affected individuals represent only a small proportion of those treated with such drugs. In many cases the mechanism for idiosyncrasy is immune mediation and is often identified by genetic risk determined by HLA variants. In the absence of diagnostic tests and/or biomarkers, the diagnosis of DILI requires a high index of suspicion after diligently excluding other causes of abnormal liver tests. Antibiotics are the class of drugs most frequently associated with idiosyncratic DILI, though recent studies indicate that herbal and dietary supplements are an increasingly recognised cause. It is imperative that upon development of DILI the culprit drug be discontinued especially in the presence of elevated transaminases (AST/ALT ≥5ULN) and/or jaundice. Risk factors for the development ALF include hepatocellular DILI and female gender, the treatment being supportive with some benefit of N-acetylcysteine in early stages. In view of the poor transplant-free survival in idiosyncratic DILI, early consideration for liver transplant is mandatory.

Keywords

Hepatotoxicity, Hepatocellular DILI, Herbal and dietary supplements, Cholestasis, Autoimmune hepatitis, Drug induced acute liver failure

Introduction

At a regulatory level drug-induced liver injury (DILI) is the commonest reason for withdrawing drugs from the market and/or issuing warnings and modification of use.[1] DILI is classified as predictable and unpredictable (idiosyncratic).[2] The former tends to be dose-related, has a short latency (days), is due to direct toxicity of the drug or its metabolite, and is reproducible in animal models (e.g. paracetamol overdose).[3] The vast majority of DILI, however, is idiosyncratic or unpredictable – it is unexpected based on the pharmacological actions of the drug and in most cases routine animal toxicology fails to identify the risk of subsequent clinical toxicity.[4] This review shall largely focus on idiosyncratic DILI.

Epidemiology

Idiosyncratic DILI is an uncommon adverse event when taking prescription or non-prescription medications. It is difficult to assess the true incidence of DILI due to different diagnostic criteria and under reporting.[5] However, recent population based studies estimate the incidence to vary between 13.9-19.1 cases per 100,000 people per year[5,6].

Data from prospective DILI registries suggest that antibiotics remain the most common cause of idiosyncratic DILI. The American DILI Network (DILIN) reported antibiotics to be implicated in 45.4% of cases.[7] Other common drug classes reported by the American DILIN were herbal and dietary supplements (HDS; 16.1% which represents a significant increase over the last 10 years), cardiovascular agents (9.8%), central nervous system agents (9.1%), anti-neoplastic agents (5.5%), and analgesics (3.7%).[7] Amoxicillin-clavulanate is the most common individual drug implicated in DILI as confirmed by both European and American studies (Table 1).[6-10] In some Asian countries however, HDS are implicated in >70% of all DILI.[11]

DILI includes the whole spectrum from asymptomatic elevation in liver tests to acute liver failure (ALF). In fact, DILI remains the most common cause of ALF in the United Kingdom (UK)[12] and United States.[13] Specifically, in the UK, paracetamol overdose causes approximately 57% of all ALF with non-paracetamol drugs accounting for a further 11%.[12] In idiosyncratic DILI approximately 4% progress to ALF, risk factors

being female gender (70%) and hepatocellular DILI (80%).[8] The drugs most commonly implicated with ALF include anti-tuberculosis therapies (ATT), HDS, sulpha-containing drugs, nitrofurantoin, phenytoin, sodium valproate, flutamide and amoxicillin-clavulanate.[8,14]

Types of DILI

Idiosyncratic DILI can be classified according to the pattern of liver tests observed – hepatocellular, cholestatic, or mixed. This classification was first established by the Council for International Organizations of Medical Sciences (CIOMS)[15] and has recently been modified by the US FDA Drug Hepatotoxicity Steering Committee.[16] Hepatocellular DILI is characterised by an alanine aminotransferase (ALT) ≥3x upper limit of normal (ULN) and ALT/ alkaline phosphatase (ALP) ratio ≥5; cholestatic DILI by an (ALP) ≥2xULN and ALT/ALP ratio of ≤2; and mixed DILI with ALT ≥3xULN, ALP ≥2xULN and ALT/ALP ratio <5 but >2. Individual drugs have dispositions toward a characteristic clinical signature, however exceptions do occur. For example, amoxicillin-clavulanate usually results in a cholestatic injury but less frequently has also been associated with ALF.[17,18]

Another way to classify idiosyncratic DILI is immune-mediated (allergic) or non-immune mediated (non-allergic).[19] If immune-mediated, the latency is shorter (one to six weeks) compared to non-immune mediated reactions (one month to one year).[1,20] However exceptions do occur with immune reactions appearing after a very long latency with drugs such as nitrofurantoin[21] or even after drug cessation (e.g. sulfonamides, erythromycin, and amoxicillin-clavulanate).[20] Immune-mediated idiosyncratic reactions can be characterized by presence of fever, rash, eosinophilia, autoantibodies (such as antinuclear and anti smooth muscle antibodies), and Stevens-Johnson syndrome (SJS). Non-immune mediated reactions lack the aforementioned characteristics and importantly, as described, tend to have a long latency period (one month to one year).[1,4,20]

Other forms of DILI include steatohepatitis (amiodarone, tamoxifen, methotrexate),[22] neoplasms [hepatic adenomas due to androgenic anabolic steroids (AAS)],[23] and vascular (nodular regenerating hyperplasia due to azathioprine).[24]

Pathogenesis

The pathogenesis of idiosyncratic DILI remains unknown but is most likely due to a complex interplay between drug (e.g. dose, duration of therapy, hepatic metabolism, lipophilicity) and host factors (e.g. age, gender, genetic polymorphisms). The drug may form a reactive metabolite that triggers DILI or may form covalent adducts with tissue proteins eliciting an immune response and subsequent DILI.[25,26]

Risk factors

Multiple factors have been found to be associated with an increased susceptibility to idiosyncratic DILI. The American DILIN found a higher prevalence of DILI in women (59% vs. 41%),[7] though this was not corroborated by the Spanish DILI registry (49% vs. 51%).[8] Potential reasons for increased female susceptibility to DILI include differences in various aspects of drug pharmacokinetics or pharmacodynamics; hormonal effects or interactions with immunomodulating agents or signaling molecules; and differences in the adverse response of the immune system to some drugs, reactive drug metabolites, or drug-protein adducts.[27] It is consistently observed, however, that women tend to be younger and develop hepatocellular DILI whereas men tend to be older and develop cholestatic DILI.[7,28]

Elderly patients have almost a three-fold increase in the incidence of DILI as shown in the study from Iceland.[6] This was attributed to the increased prescription rate of drugs in the elderly.[6] In general, higher drug dose and longer duration of therapy has also been implicated in poorer outcomes.[28-30] In the Spanish Registry, 77% of patients with idiosyncratic DILI received medications with daily doses ≥50mg.[28] Ninety percent of patients with serious DILI needing a liver transplant and reported to the Swedish Adverse Drug Reactions Advisory Committee were consuming ≥50mg/day of the drug.[29] A longer duration of drug therapy (135 ± 31 days vs. 53 ± 3 days, $p<0.0001$) has been associated with a higher liver-related morbidity and mortality.[31]

It remains controversial as to whether pre-existing liver disease increases susceptibility to idiosyncratic DILI. In the American DILIN 10% had pre-existing liver disease mostly due to hepatitis C and non-alcoholic fatty liver disease (NAFLD). This group was characterised by more severe liver injury, and higher overall mortality (16% vs. 5.2%, p<0.001) though similar liver related mortality (57% vs. 46%, p=0.5).[7] The higher overall mortality in those with pre-existing liver disease may have been due to significantly higher prevalence of comorbidity, specifically diabetes mellitus (38% vs. 23%, p=0.004).[7] Additionally, alcohol excess and/or risk factors for NAFLD increase susceptibility to methotrexate toxicity by 3-4 fold.[32] Furthermore, some studies have shown that patients with chronic hepatitis B or C could have a three-fold increased risk of abnormal liver tests after receiving ATT.[33,34] Nonetheless, the interpretation of liver injury in patients with chronic hepatitis B and C receiving ATT remains unclear – is it the ATT, reactivation/flare of the virus, or improved immune system function due to control of the tuberculosis infection leading to attack on the virus?[35]

Genetic factors also increase susceptibility to DILI. For example, HLA B*5701 confers an 80-fold increased risk to flucloxacillin induced DILI, whereas the absence of this genotype has an 88% negative predictive value for flucloxacillin-related DILI.[36]

In *Case 1* (fig 1) we present a patient who could be considered to have flucloxacillin hepatotoxicity. However, unusual features were the young age, short duration of drug use and near normal gamma-glutamyl transferase (γGT) despite significant hyperbilirubinaemia. A more detailed history revealed the use of the dietary supplement Massdrol (which is an AAS) prior to ingestion of flucloxacillin. A subsequent liver biopsy revealed bland cholestasis characteristic of AAS hepatotoxicity (fig 2).[37] His HLA genotype was B12/B42. HLA B*5701, which confers susceptibility to flucloxacillin-related hepatotoxicity,[36] was not identified.

Natural History of DILI, and Hy's Law

In the American DILIN, the presentation of DILI was with jaundice in 70% of cases. Most recovered after drug withdrawal, however 17% progressed to chronic DILI (defined as abnormal liver tests for longer than six months) and 10% needed a liver transplant and/or died.[7] Mortality increased to 44% in the presence of SJS.[7]

Compared to those with cholestatic DILI, those with hepatocellular DILI were more likely to require a liver transplant (6.2% vs. 2.9%, p<0.001) and have fatal injury (9% vs. 4%, p<0.001).[7] Furthermore, use of non-body building HDS was associated with a significantly higher need for liver transplant compared to conventional drugs (13% vs. 3%, p<0.05).[38] Worryingly, 7% of cases were attributed to HDS during the first two years of the American DILI registry compared to 20% ten years later.[38] The American Acute Liver Failure Study Group (ALFSG) also recently reported that prevalence of DILI-ALF/acute liver injury cases due to HDS increased from 1998-2007 to 2007-2015 (12.4 vs. 21.1%, p=0.047). The HDS group had higher transplantation rates (56% vs. 32%, P<0.005), and a lower transplant-free survival (17% vs. 34%, p=0.044).[39]

Specifically in hepatocellular DILI, a serum bilirubin ≥3xULN in the absence of biliary obstruction or Gilbert's syndrome is associated with a mortality of approximately 10% (range 5-50%).[40] This is also known as Hy's law, in recognition of the pioneering work done by Hyman Zimmerman – an American Hepatologist. Hy's law has now been confirmed by European and American prospective DILI registries.[7,8] Hy's law has also been adopted by the FDA as a predictor of severe DILI during clinical trials, though in the interest of patient safety the FDA has lowered the hyperbilirubinaemia required to ≥2xULN ("modified Hy's Law").[40] The FDA states that "finding one Hy's law case in the clinical trial database is worrisome; finding two is considered highly predictive that the drug has the potential to cause severe DILI when given to a larger population".[40]

Predicting those who are likely to develop ALF in idiosyncratic DILI is difficult, and even the application of Hy's law provides a specificity of only 44-67% and sensitivity of 83-90%.[8] In an attempt to improve this the Spanish DILIN developed a composite score to predict ALF: AST ≥17.3xULN; total bilirubin ≥6.6xULN, AST:ALT ≥1.5xULN. These criteria are able to determine progression to ALF with a specificity of 82% and sensitivity of 80%.[8] This composite score, however, needs to be validated in additional prospective studies.

Diagnosis

Since there are no diagnostic tests or biomarkers for idiosyncratic DILI, its diagnosis is made after stringently excluding other causes of liver disease, assessing the temporal association between use of drug and abnormal liver tests, looking for a characteristic clinical drug signature, and assessing improvement in liver tests upon drug withdrawal. Drug re-challenge is rarely indicated and cannot be advocated on ethical grounds. Nonetheless, one situation where a re-challenge may be justifiable is in the treatment of tuberculosis, however, this must only be done after carefully weighing the risks and benefits and in close liaison with a Hepatologist.[4] Finally, various causality assessment tools exist for DILI of which the Roussell Uclaf Causality Assessment Method (RUCAM) is the most utilised though it is far from perfect.[41]

Liver biopsy can be helpful in certain situations, particularly to exclude other causes of liver disease (e.g. alcohol, NAFLD). It also has a role if “drug-induced” autoimmune hepatitis (AIH) is suspected and needs differentiating from idiosyncratic DILI.[42] Portal and intra-acinar plasma cells, rosette formation, and emperiopolesis are histological features that favour AIH ($p<0.02$), whereas portal neutrophils and intracellular (hepatocellular) cholestasis are more prevalent in DILI ($p<0.02$; Table 2).[42] This differentiation is nonetheless based on retrospective data and in the real world differentiating “drug-induced AIH” from idiosyncratic DILI maybe far more difficult.

In *Case 2* (fig 1), a subsequent liver biopsy confirmed cirrhosis with lymphoplasmacytic portal inflammation and interface hepatitis. This was suggestive of AIH. While statins have been associated with DILI including “drug-induced” AIH[43], it would have been very unusual for the statin to result in cirrhosis, that too within a year.[43] This patient most likely had an underlying propensity to develop idiopathic AIH and the statin either unmasked or triggered this, or was an innocent bystander. She was treated with corticosteroids and azathioprine with good response.

Management of DILI

Prompt cessation of the culprit drug as soon as DILI is suspected is of paramount importance. There are also therapies for specific causes of DILI; for example, N-acetylcysteine (NAC) for paracetamol overdose[44] and L-carnitine for valproic acid

overdose.[45]

Corticosteroid therapy in DILI has a limited role, being reserved for those with immune-mediated DILI or “drug-induced” AIH. The former may only need a short course of steroids, whereas the latter, which is often indistinguishable from idiopathic AIH, often requires prolonged courses of steroids and/or additional immunosuppression.[46,47,48,49] As already stated, not infrequently, differentiating DILI from “drug-induced” AIH can be difficult, and in such situations after careful assessment of risks benefits a trial of corticosteroids may be warranted. Though ursodeoxycholic acid is often used in cholestatic DILI, this remains non-evidenced based.[50]

Acute Liver Failure

Case 3 (fig 1) presents a patient who has developed ALF. Pegylated interferon alpha use has not been associated with ALF. Hepatitis B and C flares were excluded by negative polymerase chain reaction; therefore, the most likely cause was clarithromycin-induced ALF. Clarithromycin has been associated with cholestatic DILI particularly in the elderly and ALF has been reported.[51] This patient was urgently listed for a liver transplant but unfortunately developed progressive cerebral oedema and died before he could be transplanted.

Spontaneous survival with ALF secondary to idiosyncratic DILI (non-paracetamol) is poor with only 27.1% of patients alive at three weeks,[14] in contrast to paracetamol-induced ALF where spontaneous survival is 64-66%.[52] Therefore it is crucial that, especially in idiosyncratic DILI, early discussion with a tertiary liver centre takes place at the first hint of ALF (worsening jaundice, coagulopathy [INR >1.5] or development of hepatic encephalopathy [HE]). With transplantation the overall survival increases to 66.2% which demonstrates the necessity to rapidly identify those with ALF due to idiosyncratic DILI.[8] The King’s College criteria are most commonly used to prioritise patients with paracetamol and idiosyncratic DILI for liver transplant.[53,54]

Two earlier randomised controlled trials (RCT) showed no benefit of corticosteroids in ALF, and even demonstrated a poorer outcome in those with DILI.[55,56] A more

recent study from the ALFSG corroborated this showing no improvement in overall survival in drug induced, indeterminate or autoimmune ALF (61% vs. 66%, p=0.41).[57] In fact, lower survival was observed in those patients with the highest Model for End Stage Liver Disease (MELD) scores (>40) after corticosteroid therapy (30% vs. 57%, p=0.03).[57]

NAC has a well established role in paracetamol-induced ALF[44] though is now also recommended in selected cases of non-paracetamol ALF. A recent RCT in patients with non-paracetamol ALF from the ALFSG demonstrated similar three-week-survival for patients given NAC versus placebo (70% vs. 66%, p=0.283).[58] However, transplant-free survival was significantly better for patients who received NAC compared to placebo (40% vs. 27%, p=0.043), but this was confined to those with early HE (52% vs. 30%, p=.010); whereas those with grade 3-4 HE had no benefit with NAC (9% vs. 22%, p=0.912).[58] DILI was the most prevalent aetiology of ALF within this study.

Conclusion

DILI includes the whole spectrum from asymptomatic and transient elevation in liver tests to ALF. DILI due to paracetamol overdose and idiosyncratic drug reactions remains the most common causes of ALF in the western world. DILI is a diagnosis of exclusion and there remains an urgent need to develop diagnostic biomarkers. Antimicrobials remain the most common cause of idiosyncratic DILI though recent studies show a significant increase in DILI due to herbal and dietary supplements. Hepatocellular DILI is more likely to progress too ALF compared with cholestatic or mixed DILI. The management of DILI is symptomatic with prompt cessation of the culprit drug and early referral for liver transplant upon the development of ALF especially in those with idiosyncratic DILI.

List of Figures

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References

1. Kaplowitz N. Idiosyncratic drug hepatotoxicity. Nat Rev Drug Discov 2005;4:489-99.

2. Kaplowitz N. Drug-induced liver injury. Clin Infect Dis 2004;38 Suppl 2:S44-8.

3. Pham TV. Acetaminophen hepatotoxicity, In: Taylor M, ed. Gastrointestinal emergencies. Baltimore (MD): Williams and Wilkins, 1997:371-88.

4. Verma S, Kaplowitz N. Diagnosis, management and prevention of drug-induced liver injury. Gut 2009;58:1555-64.

5. Sgro C, Clinard F, Ouazir K, et al. Incidence of drug-induced hepatic injuries: a French population-based study. Hepatology 2002;36:451-5.

6. Björnsson ES, Bergmann OM, Björnsson HK, Kvaran RB, Olafsson S. Incidence, presentation, and outcomes in patients with drug-induced liver injury in the general population of Iceland. Gastroenterology 2013;144:1419-25.

7. Chalasani N, Bonkovsky HL, Fontana R, et al. Features and outcomes of 899 patients with drug-induced liver injury: the DILIN prospective study. Gastroenterology 2015;148:1340-52.

8. Robles-Diaz M, Lucena MI, Kaplowitz N, et al. Use of Hy's law and a new composite algorithm to predict acute liver failure in patients with drug-induced liver injury. Gastroenterology 2014;147:109-18.

9. de Abajo FJ, Montero D, Madurga M, García Rodríguez LA. Acute and clinically relevant drug-induced liver injury: a population based case-control study. Br J Clin Pharmacol 2004;58:71-80.

10. Andrade RJ, Lucena MI, Fernández MC, et al. Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish registry over a 10-year period. Gastroenterology 2005;129:512-21.

11. Suk KT, Kim DJ, Kim CH, et al. A prospective nationwide study of drug-induced liver injury in Korea. Am J Gastroenterol 2002;107:1380-7.

12. Bernal W, Wendon J. Acute liver failure. N Engl J Med 2013;369:2525-34.

13. Lee WM. Acute liver failure in the United States. Semin Liver Dis 2003;23:217-26.

14. Reuben A, Koch DG, Lee WM, Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology 2010;52:2065-76.

15. Bénichou C. Criteria of drug-induced liver disorders. Report of an international consensus meeting. J Hepatol 1990;11:272-6.

16. Navarro V. Hepatic adverse event nomenclature document (online). Available from URL: http://www.fda.gov/downloads/Drugs/ScienceResearch/.../ucm080365.ppt. Accessed 29th April, 2016.

17. Salvo F, Polimeni G, Moretti U, et al. Adverse drug reactions related to amoxicillin alone and in association with clavulanic acid: data from spontaneous reporting in Italy. J Antimicrob Chemother 2007;60:121-6.

18. Beraldo DO, Melo JF, Bonfim AV, et al. Acute cholestatic hepatitis caused by amoxicillin/clavulanate. World J Gastroenterol 2013;19:8789-92.

19. Obermayer-Straub P and Manns MP, In: Kaplowitz N and DeLeve L, eds. Drug induced liver disease. New York: Marcel Dekker, 2003:125-149.

20. Abboud G, Kaplowitz N. Drug-induced liver injury. Drug Saf 2007;30:277-94.

21. Sakaan SA, Twilla JD, Usery JB, et al. Nitrofurantoin-induced hepatotoxicity: a rare yet serious complication. South Med J 2014;107:107-13.

22. Amacher DE, Chalasani N. Drug-induced hepatic steatosis. Semin Liver Dis 2014;42:205-14.

23. Gorayski P, Thompson CH, Subhash HS, Thomas AC. Hepatocellular carcinoma associated with recreational anabolic steroid use. Br J Sports Med 2008;42:74-5.

24. Musumba CO. Review article: the associated between nodular regenerative hyperplasia, inflammatory bowel disease and thiopurine therapy. Aliment Pharmacol Ther 2013;38:1025-37.

25. Chen M, Borlak J, Tong W. High lipophilicity and high daily dose of oral medications are associated with significant risk for drug-induced liver injury. Hepatology 2013;58:388-96.

26. Fontana RJ. Pathogenesis of idiosyncratic drug-induced liver injury and clinical perspectives. Gastroenterology 2014;146:914-28.

27. Amacher DE. Female gender as a susceptibility factor for drug-induced liver injury. Hum Exp Toxicol 2014;33:928-39.

28. Lucena MI, Andrade RJ, Kaplowitz N, et al. Phenotypic characterization of idiosyncratic drug-induced liver injury: the influence of age and sex. Hepatology 2009;49:2001-9.

29. Lammert C, Einarsson S, Saha C, et al. Relationship between daily dose of oral medications and idiosyncratic drug-induced liver injury: search for signals. Hepatology 2008;47:2003-9.

30. Russo MW, Galanko JA, Shrestha R, Fried MW, Watkins P. Liver transplantation for acute liver failure from drug induced liver injury in the United States. Liver Transpl 2004;10:1018-23.

31. Björnsson E, Davidsdottir L. The long-term follow-up after idiosyncratic drug-induced liver injury with jaundice. J Hepatol 2009;50:511-7.

32. Rosenberg P, Urwitz H, Johannesson A, et al. Psoriasis patietns with diabetes type 2 are at high risk of developing liver fibrosis during methotrexate treatment. J Hepatol 2007;46:1111-8.

33. Chien JY, Huang RM, Wang JY, et al. Hepatitis C virus infection increases hepatitis risk during anti-tuberculosis treatment. Int J Tuberc Lung Dis 2010;14:616-21.

34. Wong WM, Wu PC, Yuen MF, et al. Antituberculosis drug-related liver dysfunction in chronic hepatitis B infection. Hepatology 2000;31:201-6.

35. Verma S and Kaplowitz N. Hepatotoxicity of antituberculosis drugs. In: Kaplowitz N and DeLeve LD, eds. Drug induced liver disease. Informa Healthcare, 2013:483-504.

36. Daly AK, Donaldson PT, Bhatnagar P, et al. HLA-B*5701 genotype is a major determinant of drug-induced liver injury due to flucloxacillin. Nat Genet 2009;41:816-9.

37. El Sherrif Y, Potts JR, Howard MR, et al. Hepatotoxicity from anabolic androgenic steroids marketed as dietary supplements: contribution from ATP8B1/ABCB11 mutations? Liver Int 2013;33:1266-70.

38. Navarro VJ, Barnhart H, Bonkovsky HL, et al. Liver injury from herbals and dietary supplements in the U.S. Drug-Induced Liver Injury Network. Hepatology 2014;60:1399-408.

39. Hillman L, Gottfried M, Whitsett M, et al. Clinical features and outcomes of complementary and alternative medicine induced acute liver failure and injury. Am J Gastroenterol 2016; [Epub ahead of print].

40. United States Food and Drug Administration. Drug-induced liver injury: premarketing clinical evaluation. 2009. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

41. Danan G, Benichou C. Causality assessment of adverse reactions to drugs. A novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries. J Clin Epidemiol 1993;46:1323-30.

42. Suzuki A, Brunt EM, Kleiner DE, et al. The use of liver biopsy evaluation in discrimination of idiopathic autoimmune hepatitis versus drug-induced liver injury. Hepatology 2011;54:931-9.

43. Russo MW, Hoofnagle JH, Gu J, et al. Spectrum of statin hepatotoxicity: experience of the drug-induced liver injury network. Hepatology 2014;60:679-86.

44. Polson J, Lee WM, American Association for the Study of Liver Disease. AASLD position paper: the management of acute liver failure. Hepatology 2005;41:1179-97.

45. Bohan TP, Helton E, McDonald I, et al. Effect of L-carnitine treatment for valproate-induced hepatotoxicity. Neurology 2001;56:1405-9.

46. Björnsson ES, Talwalkar J, Treeprasertsuk S, et al. Drug-induced autoimmune hepatitis: clinical characteristics and prognosis. Hepatology 2010;51:2040-8.

47. Weiler-Normann C, Schramm C. Drug induced liver injury and its relationship to autoimmune hepatitis. J Hepatol 2011;55:747-9.

48. Yeong T, Lim KHJ, Goubet S, Parnell N, Verma S· Natrural History and Outcomes in Drug Induced Autoimmune Hepatitis. Hepatology Research Hepatol Res. 2016;46:E79-88

49. Heurgué A, Bernard-Chabert B,DieboldMet al. Drug-induced autoimmune hepatitis: a frequent disorder. Gut 2007 56(Suppl III): A271.

50. Studniarz M, Czubkowski P, Cielecka-Kuszyk J, et al. Amoxicillin/clavulanic acid-induced cholestatic liver injury after pediatric liver transplantation. Ann Transplant 2012;17:128-31.

51. Maggi P, Solarino B, Cassano P, et al. Fatal fulminant hepatitis following administration of clarithromycin in a patient chronically treated with antipsychotic drugs. Immunopharmacol Immunotoxicol 2013;35:191-4.

52. Fontana RJ. Acute liver failure including acetaminophen overdose. Med Clin North Am 2008;92:761-94.

53. O'Grady JG, Alexander GJ, Hayllar KM, Williams R. Early indicators of prognosis in fulminant hepatic failure. Gastroenterology 1989;97:439-45.

54. McPhail MJ, Wendon JA, Bernal W. Meta-analysis of performance of King's College Hospital Criteria in prediction of outcome in non-paracetamol-induced acute liver failure. J Hepatol 2010;53:492-9.

55. Raklea J, Mosley JW, Edwards VM, Govindarajan S, Alpert E. A double-blinded, randomized trial of hydrocortisone in acute hepatic failure. The Acute Hepatic Failure Study Group. Dig Dis Sci 1991;36:1223-8.

56. EASL. Randomised trial of steroid therapy in acute liver failure. Report from the European Association for the Study of the Liver (EASL). Gut 1979;20:620-3.

57. Karkhanis J, Verna EC, Chang MS, et al. Steroid use in acute liver failure. Hepatology 2014;59:612-21.

58. Lee WM, Hynan LS, Rossaro L, et al. Intravenous N-acetylcysteine improves transplant-free survival in early stage non-acetaminophen acute liver failure. Gastroenterology 2009;137:856-64.

Common drugs implicated in idiosyncratic DILI according to studies from different countries

Iceland[6]	**American DILIN**[7]	**Spanish Registry**[8]	**UK**[9]
Amoxicillin-clavulanate	Amoxicillin-clavulanate	Amoxicillin-clavulanate	Amoxicillin-clavulanate
Diclofenac	Isoniazid	Isoniazid	Diclofenac
Azathioprine	Nitrofurantoin	Combined anti-tuberculous therapy	Tricyclic antidepressants
Infliximab	Trimethoprim-sulfamethoxazole	Flutamide	Macrolides
Nitrofurantoin	Minocycline	Ibuprofen	Chlorpromazine

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Table 2: Comparison of idiosyncratic DILI, "drug-induced" autoimmune hepatitis and *idiopathic* autoimmune hepatitis. [46,47,48,49]

	Idiosyncratic DILI	**"Drug induced" AIH**	***Idiopathic* AIH**
Histology	Portal neutrophils, intracellular cholestasis	Interphase hepatitis, plasma cells, emperipolesis, rosettes	Interphase hepatitis, plasma cells, emperipolesis, rosettes
Rash, eosinophilia	-/+	-	-
Fibrosis	+/-	+	++
Response to steroids	-	+	+
Relapse on steroid withdrawal	-	+/-	+

AIH = autoimmune hepatitis.

Case 1.
A 33-year-old male was admitted with a two-week history of jaundice. He was prescribed a five day course of flucloxacillin three weeks ago for an ingrown toenail.

Investigations demonstrated: bilirubin 120 µmol/L (peak 614 µmol/L), AST 244 iu/L, ALT 312 iu/L, ALP 130 iu/L, γGT 72 iu/L, INR 1.0. Liver screen including viral serology and imaging were unremarkable.

Case 2.
A 62-year-old female was referred for abnormal liver tests: ALT 125 iu/L, ALP 245 iu/L. On examination she had stigmata of chronic liver disease, and further investigation revealed a positive anti-smooth muscle antibody and elevated immunoglobulins, specifically IgG. Imaging confirmed cirrhosis. She had commenced a statin one year ago.

Case 3.
A 55-year-old male, co-infected with the hepatitis B (inactive carrier) and hepatitis C virus was 4 months into a six-month course of pegylated interferon alpha and ribavirin. He was non-cirrhotic and thus far had shown an excellent response to antivirals with a normal liver panel and negative hepatitis B and C PCR. He was subsequently prescribed a seven-day course of clarithromycin for a chest infection and presented a week later with jaundiced and confusion.

Investigations demonstrated: bilirubin 350 µmol/L, ALT 2000 iu/L, INR 3.0. Liver screen including viral PCR and imaging were unremarkable.

Fig 1: Three cases of DILI – what is the diagnosis and management? Each case will be discussed in the manuscript. Bilirubin range = 5-17µmol/L, AST = aspartate aminotransferase (range = 10-40 iu/L), ALT = alanine aminotransferase (range = 7-56 iu/L), ALP = alkaline phosphatase (range = 45-115 iu/L), γGT = gamma-glutamyl transferase (range = 9-48 iu/L), INR = international normalised ratio (range = 0.8-1.2), PCR = polymerase chain reaction.