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Drug-induced Liver Injury is Frequently Associated with Severe Cutaneous Adverse Drug Reactions: Experience from Two Australian Tertiary Hospitals

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/imj.13734

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Word Count Abstract: 250

Word Count Main Text: 2621

Tables: 4

Figures: 0

There were no conflicts of interest or funding sources for this work.

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Introduction

Cutaneous adverse drug reactions (cADR) represent a heterogeneous group of delayed-type hypersensitivity reactions and are associated with significant morbidity and mortality.[1-3] These include severe conditions such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP), linear IgA bullous dermatosis (LABD), and less severe manifestations such as erythema multiforme (EM).

Drug-induced liver injury (DILI) represents hepatocyte or intrahepatic biliary duct damage, either as a direct toxic effect of drugs or through immune-mediated mechanisms.[4] DILI may be a result of prescription medications, over the counter medications or herbal products.[4] DRESS is a syndrome characterised by immune-mediated multi-organ injury[5] and is well-known to be associated with liver involvement in up to 75-86% of cases[5, 6]. Furthermore, Devarbhavi *et al*.[7] determined that DILI is a common association with SJS/TEN and mortality is higher in SJS/TEN patients with DILI. However, overall, the frequency of DILI in patients with severe cADR conditions is not well understood and the clinico-biochemical characteristics of these patients are poorly established.

The aim of this study is to determine the prevalence of DILI and the severity and patterns of liver injury in patients with severe cADR. The secondary objectives are to identify associated factors for the development of DILI in patients with severe cADR, to assess the spectrum of implicated drugs and to determine drug causality. Finally, we aim to compare the clinical outcomes of patients who developed cADR-associated DILI with those in whom DILI did not occur.

Materials and Methods

This was a retrospective cohort study conducted at two tertiary hospitals in metropolitan Melbourne, Victoria, Australia using data spanning 10 years. The Alfred Hospital is a 350-bed university-affiliated referral hospital, which provides the state-wide Burns Service. The Austin Hospital is a 560-bed university affiliated hospital providing the state-wide Liver Transplantion and Spinal Services. Institutional ethics approval was obtained (Alfred Hospital project approval: 561/15 and Austin Hospital project approval: 15/465).

Inpatients diagnosed with a severe cADR over a ten-year period (from 1st January 2004 to 31st August 2014) were identified through the hospitals' adverse drug reaction notifications and International Statistical Classification of Diseases and Related Health Problems (ICD-10) coding.[8] Burns, Human Immunodeficiency Virus (HIV) and Liver Transplant databases were also cross-examined to capture additional cases. All cases of cADR were diagnosed and confirmed through clinical and histopathological assessment by the hospital dermatology and pathology services. Patients who were managed exclusively as outpatients or with skin reactions attributed to non-drug causes were excluded from the analysis. Patient demographics, comorbidities, cADR type, causative drugs, pattern and severity of liver injury, laboratory investigations during admission, length of hospitalisation and inpatient mortality were collected. Drug causality for cADR conditions was assessed by consensus decision-making based on the Naranjo score[9] and the ALDEN score[10] and the by the Adverse Drug Reaction Review Committees at both sites. To further determine the causality of DILI, each suspect medication was assigned a score by Roussel Uclaff Causality Assessment Method (RUCAM).[11] The RUCAM score is currently the most widely accepted DILI causality assessment algorithm.[12] It consists of seven components: time to onset, course of liver function tests (LFTs) after cessation of drug, presence of risk factors for DILI, presence of concomitant drug, presence of other causes of liver injury, previous information on hepatotoxicity and response to re-administration. It has been validated to have 86% sensitivity and 89% specificity.[11]

The RUCAM scoring was performed by study investigators (WF, AA, LG, NRA and CG) and discrepancies were resolved by consensus. If more than one medication was implicated in the cADR in a patient, only the medication with the highest RUCAM score was considered in the concordance analysis with the ALDEN score.

Definitions

The types of cutaneous eruptions included in our cADR definition were SJS, TEN, SJS/TEN overlap, DRESS, AGEP, EM and LABD. SJS was defined as mucocutaneous blistering with skin detachment affecting less than 10% of body surface areas (BSA), TEN if skin detachment was greater than 30% BSA, and SJS-TEN overlap for 10-30% of BSA involvement.[13] DRESS was defined as per RegiSCAR criteria.[5]

DILI definitions were based on criteria published by Aithal *et al*.[14] DILI was defined as ≥5x upper limit of normal (ULN) for alanine aminotransferase (ALT), or ≥2 ULN for alkaline phosphatase (ALP), or ≥3 ULN for ALT with bilirubin ≥2 ULN. The pattern of DILI was defined using the R value where R = (ALT/ULN)/(ALP/ULN), calculated on the earliest identified deranged liver function tests. An R score of 2 or less was classified as cholestatic, between 2 and 5 mixed and greater than 5, hepatocellular. The severity of DILI was determined using the degree of elevation of enzyme levels and clinical features of liver impairment (Table. 1). Acute liver failure was defined as liver injury with encephalopathy and an INR ≥1.5 with the duration of illness <26 weeks.[15] Peripheral lymphocytosis was defined as >3.3 $x10^9$ lymphocytes/litre in peripheral blood, in accordance with the laboratory cut-off values. In terms of causality association, the RUCAM score of <3 was considered 'unlikely', 3 – 5 'possible', 6 – 8 'probable' and >8 'highly probable'.[11]

Statistical Analysis

Data was evaluated for normality of distribution and descriptive statistics were calculated using percentages and medians (interquartile ranges). Wilcoxon rank sum and Fisher's exact

tests were used for univariate analyses to detect the differences in characteristics between the group of patients with cADR-associated DILI and those without associated DILI and to derive odds ratios (OR) (GraphPad Prism 6, GraphPad Software, Inc., California, USA). A two-tailed P-value of <0.05 was considered statistically significant for all associations.

Results

This study included 111 patients diagnosed with severe cADR. Of those, 7 patients were excluded as their cutaneous reaction was attributed to non-drug causes. Of the 104 subjects included, 76 (73.1%) had SJS/TEN, 12 (11.5%) had DRESS, 11 (10.6%) had AGEP, 3 (2.9%) had EM and 2 (1.9%) had LABD. The median age of patients was 53 [Interquartile range (IQR) 39-67] years and 57.7% were male.

Of the 104 patients with severe cADR, 33 (31.7%) had associated DILI. This represented 30.2% of patients with SJS/TEN, 50% of patients with DRESS and 18.2% of patients with AGEP. One patient with EM and one patient with LABD also met DILI criteria.

In terms of the patterns of liver injury, 23 (69.7%) had a mixed/cholestatic pattern and 10 (30.3%) had a hepatocellular pattern of injury. With respect to severity, 23 (69.7%) patients had mild, 2 (6.1%) had moderate and 6 (18.2%) had severe DILI. No significant differences in underlying risk factors for chronic liver disease were noted between those who had DILI and those who did not (Table 2). At presentation, biochemical abnormalities commonly associated with development of DILI included lower haemoglobin and albumin values, and higher GGT and ALT values (Table 3).

After excluding 2 patients with incomplete results, a positive association was seen between developing DILI and the presence of peripheral lymphocytosis and eosinophilia; 45.5% of patients with DILI were noted to have peripheral lymphocytosis noted during their admission,

compared to 14.5% of those without (OR 4.9, 95% CI 1.88 – 12.8, p=0.012), and 54% of patients with DILI had eosinophilia present during their admission, compared to only 29% of patients without (OR 2.9, 95% CI 1.24 – 6.95, p=0.016).

Of the 33 subjects who developed DILI, a total of 59 medications were implicated in their cADR-associated liver injury (Table 4). Antimicrobials were implicated in 62.7% and beta-lactams were the most common class (14, 23.7%). RUCAM score was ≥3 (at least 'possible' causal association) in 69.7% (23/33) of subjects for at least one medication. The medication with the highest Naranjo or ALDEN score (implicated as the causal medication in the cADR) was concordant with the medication with the highest RUCAM score (implicated in causing DILI) in 81.8% (27/33) of subjects.

The median length of stay for cADR patients with DILI was significantly longer than those without DILI (19 days vs. 11 days, P=0.002). Inpatient mortality occurred in 5 patients (15.2%) with DILI (4 had SJS/TEN, 1 had AGEP) and 7 patients (9.9%) without (all 7 had SJS/TEN) [Odds Ratio (OR) 1.6, 95% CI: 0.48-5.6, P=0.43]. Two patients with severe DILI also met the definition for acute liver failure: one had SJS/TEN, was admitted to ICU and died, and the other had DRESS, responded to prednisolone and survived. No patients required liver transplantation, and the patient who died in ICU was not considered for liver transplantation due to multi-organ failure and poor neurological recovery after severe cADR.

Subgroup Analysis

A subgroup analysis of patients with SJS/TEN was undertaken, as this group comprised the majority of patients with cADR. Of the 23 patients with SJS/TEN who developed DILI, 5 (21.7%) met the definition for severe liver injury. The predominant pattern of liver injury was mixed/cholestatic, occurring in 65% of cases. The RUCAM result was 'possible'/'probable' (e3) in 17 of 22 (77.3%) patients, and the score could not be calculated in one patient. The medication with the highest RUCAM score was also the medication with the highest Naranjo or ALDEN score in 81.8% (18 out of 22) of cases. In patients with SJS/TEN, peripheral

lymphocytosis was noted to occur more frequently in patients with DILI than in those without DILI (43.4% vs. 11.3%, OR=6, 95% CI 1.8-19.7, P=0.003).

Discussion

While liver injury is known to be associated with certain cADR conditions (particularly, DRESS), there has been limited research investigating the prevalence of DILI in patients with other severe cADRs, such as SJS/TEN.[16, 17] Our study demonstrated that up to a third of patients with severe cADR conditions have concurrent DILI. We also found that DILI was common in patients with SJS/TEN and was present in up to 30%.

The reported prevalence of liver dysfunction in cutaneous drug eruptions is between 75 - 86% in DRESS[5, 6] and around 37% in SJS/TEN.[17] However, the reported prevalence varied due to differing contemporaneous definitions of DILI employed in those studies, with differing cut-off values for LFTs. In this study, we employed the definition by Aithal *et al*., which is a widely accepted and validated definition.[14] Utilising this definition, we ascertained that DILI is commonly associated with severe cADR and that a majority of patients had mixed or cholestatic pattern of injury.[6, 7] We also found that whilst almost one in five patients with liver dysfunction had severe DILI, the acute liver failure rate was low, and none needed transplant.

We attempted to identify significant clinical associations (*i.e.* age, gender, history of chronic liver disease, viral hepatitides, HIV, excess alcohol consumption) as potential predictors for developing cADR-associated DILI but found none in univariate models (Table 2). However, significant associations between DILI and certain haematological and biochemical values were seen (Table 3). The higher GGT and ALP levels in the DILI group likely reflected the liver injury that was already present at the time of presentation, whilst lower haemoglobin and albumin levels in DILI patients were likely multifactorial in nature and may be representative of stress induced by a concurrent DILI or severe cADR, but may also reflect critical illness, cytokine release in inflammatory illness, catabolism and malnutrition.[18-20]

The spectrum of implicated drugs was also generally similar to those described in comparable studies [6, 7, 17] with aromatic anticonvulsants, sulphonamides, nevirapine and beta-lactams being common causative agents. We found that although beta-lactams were the most common antibiotics implicated, vancomycin was the single antibiotic most frequently associated with both cADR and DILI. Whether this reflects a bias towards higher usage of vancomycin in the tertiary referral hospitals, or other confounders attributing to this association, warrants further exploration.

Liver dysfunction is common in acutely unwell patients. Concurrent non-drug related mechanisms such as sepsis-associated cholestasis[21], systemic inflammatory response syndrome[22] or ischaemic hepatitis secondary to hypotension are common contributing factors, as opposed to direct drug-related pharmacodynamics/pharmacokinetics[4], pharmacogenomics or immunological mechanisms. To clarify these, we calculated the RUCAM scores, which takes into account above confounding factors, such as concurrent liver ischaemia, and has been validated to have positive predictive values of 93% for drug causality.[12] We found that almost 70% of patients with DILI had at least one drug implicated as 'possible' or 'probable' causality, implying that direct drug-injury is the more likely mechanism in the majority of patients. This was also confirmed by a high overall concordance rate (82%) between the highest RUCAM and Naranjo/ALDEN scores for the same culprit drug.

However, an important aspect to note is that RUCAM takes into account 'drug rechallenge' as a category on its own and assigns a probability score based on whether or not there is recurrence of liver injury upon 'rechallenge'. 'Drug rechallenge' is not currently recommended in patients with severe cADRs due to risk of severe reactions or even death upon re-exposure.[23] Therefore, none of the patients in this study underwent 'rechallenge' and this may have resulted in lower RUCAM scores of the entire cohort, with 7 patients having a score of <3, thereby under-estimating the actual strength of causal associations. This raises an interesting question as to whether RUCAM assessment method needs to be further modified

and validated, especially in patients with severe cADR conditions and concurrent DILI, to better establish drug causality.

The higher rates of peripheral lymphocytosis and eosinophilia in patients with cADR and DILI are noteworthy findings. The higher prevalence of eosinophilia in those with cADR and DILI is expected, and attributed to the significant proportion of patients with DRESS studied (11.5%). Moreover, when all patients with DRESS were removed from the analysis, the association between developing DILI and peripheral eosinophilia becomes statistically insignificant. However, the association between the higher rates of peripheral lymphocytosis and developing DILI is novel. Subgroup analysis of the most prevalent cADR in our study (SJS/TEN) confirms that developing DILI is associated with peripheral lymphocytosis. This may reflect a common T-cell mediated pathophysiological process occurring in both skin and liver, a generalised state of severe immune activation, or undetected viral infections or reactivations contributing to disease manifestations. SJS/TEN is a process mediated by cytotoxic CD8+ and natural killer (NK) cells resulting in granulysin production and Fas-Fas Ligand activation, causing apoptosis of the epidermis in skin and mucous membranes.[24] Similarly, infiltrates of CD8+ T cells have been detected on histopathological studies in patients with DILI to common drugs such as amoxicillin/clavulanate and lamotrigine.[25] Moreover, the role of herpes virus [Epstein-Barr virus, cytomegalovirus, human herpes viruses (HHV) 6 and 7] reactivation in the pathogenesis of cADRs has also recently been increasingly recognised.[26] Lin *et al.*[6] demonstrated that atypical lymphocytosis was more frequently seen in DRESS patients with liver injury, with HHV reactivation being one of the postulated mechanisms, along with direct immunologic mechanisms of injury (T-cell mediated or cytokine release). Unfortunately, very few patients in our study had viral studies performed or the presence of atypical lymphocytosis determined (data not presented). Future studies incorporating flow cytometry utilising T-cell activation markers, such as CD137, and specific cytokine profiling, such as interferon gamma, tumour necrosis factor alpha and

granulysin from peripheral blood and lymphocyte marker immunohistochemistry, as well as herpes virus studies, in all serum, skin and liver biopsies may clarify the underlying immunopathological mechanisms and associations.

Our study has several limitations. Firstly, the number of patients included for each cADR condition was small and this might have resulted in lack of significant findings on clinico-biochemical associations. Nevertheless, this study included the largest cohort of SJS/TEN patients to date. Secondly, given that only inpatients from two tertiary referral hospitals serving as state-wide burns and liver transplant centres were studied, the severe end of the disease spectrum may be over-represented, especially for SJS/TEN, and therefore the prevalence of DILI over-estimated. This may influence the generalisability and representativeness of our results. Nevertheless, we found that despite the severity of their cutaneous conditions, most patients had only mild to moderate DILI, mortality rate was low and none underwent liver transplantation. Lastly, the retrospective nature of this cohort study poses further inherent limitations on important data such as viral studies and presence of atypical lymphocytosis. We recommend that given the uncommon nature of these reactions, future studies should be conducted through a collaborative and systematised framework of data acquisition through combined registries in order to increase statistical power in translating scientific discovery into better understanding of immunopathologic mechanisms, prevention, and improved outcomes for patients.

Conclusion

DILI is commonly associated with severe cADR conditions, especially DRESS and SJS/TEN. Patients with cADR-associated DILI have a significantly longer hospital length of stay. The group of drugs implicated in cADR-associated DILI is heterogeneous, but there may be a common pathogenic pathway affecting both organs. Our finding of a higher frequency of peripheral lymphocytosis in patients with SJS/TEN associated DILI warrants further *in vivo* and *in vitro* studies.

Acknowledgements

We would like to acknowledge the Alfred Health Adverse Drug Reaction Review Committee, Austin Adverse Drug Reaction Committee, State Burns and HIV units in allowing the access of their databases.

References

1. Mahar PD, Wasiak J, Hii B, Cleland H, Watters DA, Gin D, Spinks AB. A systematic review of the management and outcome of toxic epidermal necrolysis treated in burns centres. Burns 2014; 40:1245-54.

2. Cacoub P, Musette P, Descamps V, Meyer O, Speirs C, Finzi L, Roujeau JC. The DRESS syndrome: a literature review. The American journal of medicine 2011; 124:588-97.

3. Chen Y-C, Chiu H-C, Chu C-Y. Drug reaction with eosinophilia and systemic symptoms: a retrospective study of 60 cases. Arch Dermatol 2010; 146:1373-9.

4. Fisher K, Vuppalanchi R, Saxena R. Drug-induced liver injury. Arch Pathol Lab Med 2015; 139:876-87.

5. Kardaun S, Sekula P, Valeyrie -Allanore L, Liss Y, Chu Sidoroff A, Naldi L, Mockenhaupt M, Roujeau J. Drug reaction with eosinophilia and systemic symptoms (DRESS): an original multisystem adverse drug reaction. Results from the prospective RegiSCAR study. Br J Dermatol 2013; 169:1071-80.

6. Lin I-C, Yang H-C, Strong C, Yang C-W, Cho Y-T, Chen K-L, Chu C-Y. Liver injury in patients with DRESS: A clinical study of 72 cases. J Am Acad Dermatol 2015; 72:984-91.

7. Devarbhavi H, Raj S, Aradya VH, Rangegowda VT, Veeranna GP, Singh R, Reddy V, Patil M. Drug -induced liver injury ass syndrome/toxic epidermal necrolysis: Patient characteristics, causes, and outcome in 36 cases. Hepatology 2016; 63:993-9.

8. Graudins LV, Ly J, Trubiano J, Aung AK. More than skin deep. Ten year follow -up of delayed cutaneous adv Pharmacol 2016; 82:1040-7.

9. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts E, Janecek E, Domecq C, Greenblatt D. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981; 30:239.

10. Sassolas B, Haddad C, Mockenhaupt M, Dunant A, Liss Y, Bork K, Haustein U, Vieluf D, Roujeau J, Le Louet H. ALDEN, an algorithm for assessment of drug causality in Stevens–Johnson syndrome and toxic epidermal necrolysis: comparison with case–control analysis. Clin Pharmacol Ther 2010; 88:60-8.

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

12. García-Cortés M, Stephens C, Lucena MI, Fernández-Castañer A, Andrade RJ. Causality assessment methods in drug induced liver injury: strengths and weaknesses. J Hepatol 2011; 55:683-91.

13. Mockenhaupt M. The current understanding of Stevens-Johnson syndrome and toxic epidermal necrolysis. Expert Rev Clin Immunol 2011; 7:803.

14. Aithal G, Watkins P, Andrade R, Larrey D, Molokhia M, Takikawa H, Hunt C, Wilke R, Avigan M, Kaplowitz N. Case definition and phenotype standardization in drug -16duced liver injury. Clin Pharmacol Th

15. Lee WM, Stravitz RT, Larson AM. Introduction to the revised American Association for the Study of Liver Diseases Position Paper on acute liver failure 2011. Hepatology 2012; 55:965-7.

16. Revuz J, Penso D, Roujeau J-C, Guillaume J-C, Payne CR, Wechsler J, Touraine R. Toxic epidermal necrolysis: clinical findings and prognosis factors in 87 patients. Arch Dermatol 1987; 123:1160-5.

17. Lee T, Lee YS, Yoon S-Y, Kim S, Bae Y-J, Kwon H-S, Cho YS, Moon H-B, Kim T-B. Characteristics of liver injury in drug-induced systemic hypersensitivity reactions. J Am Acad Dermatol 2013; 69:407-15.

18. Hayden SJ, Albert TJ, Watkins TR, Swenson ER. Anemia in critical illness: insights into etiology, consequences, and management. Am J Respir Crit Care Med 2012; 185:1049-57.

19. Nicholson J, Wolmarans M, Park G. The role of albumin in critical illness. Br J Anaesth 2000; 85:599-610.

20. Helliksson F, Wernerman J, Wiklund L, Rosell J, Karlsson M. The combined use of three widely available biochemical markers as predictor of organ failure in critically ill patients. Scand J Clin Lab Invest 2016; 76:479-85.

21. Chand N, Sanyal AJ. Sepsis -induced cholestasis. 41.

22. Angus DC, Van der Poll T. Severe sepsis and septic shock. N Engl J Med 2013; 369:840-51.

23. Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. N Engl J Med 1994; 331:1272-85.

24. Nassif A, Bensussan A, Boumsell L, Deniaud A, Moslehi H, Wolkenstein P, Bagot M, Roujeau J-C. Toxic epidermal necrolysis: effector cells are drug-specific cytotoxic T cells. J Allergy Clin Immunol 2004; 114:1209-15.

25. Foureau D, Walling T, Maddukuri V, Anderson W, Culbreath K, Kleiner D, Ahrens W, Jacobs C, Watkins PB, Fontana R. Comparative analysis of portal hepatic

infiltrating leucocytes in acute drug -induced liver inju

viral hepatitis. Clin Exp Immunol 2015; 180:40-51.

26. Adler NR, Aung AK, Ergen EN, Trubiano J, Goh MS, Phillips EJ. Recent advances in the understanding of severe cutaneous adverse reactions. Br J Dermatol 2017.

Tables

Table 1. Drug-Induced Liver Injury Severity Index[14]

Category	Severity	Description
1	**Mild**	Elevated ALT/ALP concentration reaching criteria for DILI, but bilirubin concentration <2x ULN
2	**Moderate**	Elevated ALT/ALP concentration reaching criteria for DILI and bilirubin concentration e2x ULN, or symptomatic hepatitis
3	**Severe**	Elevated ALT/ALP concentration reaching criteria for DILI, bilirubin concentration e2x ULN and one of the following: International normalised ratio (INR) e1.5, ascites and or encephalopathy, disease duration <26 weeks and absence of underlying cirrhosis/other organ failure considered to be due to DILI
4	**Fatal/Transplant**	Death or liver transplantation due to DILI

Table 2. Comparison of Risk Factors for Development of DILI in Patients with cADR

	cADR with DILI (n=33)	cADR without DILI (n=71)	P-value
Median age, years (IQR)	55 (45 - 66)	50 (35– 67.5)	0.23
Male gender, n (%)	19 (57.6%)	41 (57.7%)	1.00
Hepatitis B[†], n (%)	0 (0%)	0 (0%)	1.00
Hepatitis C[‡], n (%)	4 (12.1%)	4 (5.6%)	0.26
HIV[§] n (%)	3 (9.1%)	4 (5.6%)	0.67
Excess alcohol consumption[¶], n (%)	3 (9.1%)	11 (15.5%)	0.54
Chronic liver disease [Δ], n (%)	2 (6.1%)	4 (5.6%)	1.00

[†] Acute or chronic hepatitis B infection as denoted by past medical history or positive hepatitis B surface antigen or hepatitis B core antibody
[‡] Active or previous hepatitis C infection as denoted by past medical history, positive serology or RNA titres
[§] Human immunodeficiency virus
[¶] Excess alcohol consumption is defined as more than 2 standard drinks per day on average over a 12-month period
[Δ] Chronic liver disease is defined as history of cirrhosis, chronic viral hepatitis, autoimmune hepatitis, alcoholic liver disease, fatty liver disease or genetically related liver disease

Table 3. Baseline Laboratory Values (Median and IQR)

Investigation	Normal Range	cADR alone (IQR)	cADR and DILI (IQR)	P-Value
Haemoglobin (g/L)	120-150	130 (117-140)	112 (97-124)	**0.0029**
WCC[†] ($\times 10^9$/L)	4-10	7.8 (4.7-14)	7.4 (5.8-12.8)	0.69
Platelets ($\times 10^9$/L)	150-410	227 (163-302)	181 (129-173)	0.051
Creatinine (μmol/L)	45-90	71 (55-87)	84 (61-143)	0.14
Albumin (g/L)	34-47	30 (27-35)	28 (24-30)	**0.035**
Bilirubin (μmol/L)	<22	10 (7-15)	11 (8-16)	0.41
ALT[‡] (IU/L)	5-30	29 (20-53)	38 (38-122)	0.088
GGT[§] (IU/L)	6-42	47 (25-92)	95 (61-185)	**0.0023**
ALP[¶] (IU/L)	30-110	77 (56.5-97)	103 (83-647)	**0.0011**
INR	0.9-1.2	1.2 (1.1-1.3)	1.3 (1.1-1.4)	0.061

[†] White cell count
[‡] Alanine aminotransferase
[§] Gamma-glutamyl transferase
[¶]Alkaline phosphatase
[Δ] International normalised ratio

Table 4. All Drugs Implicated in DILI

Classes	Drugs	N = 59
Antimicrobials (n = 37)	Cephalosporins	8
	Vancomycin	7
	Penicillins	6
	Nevirapine	3
	Trimethoprim/Sulfamethoxazole	3
	Fluconazole	2
	Ciprofloxacin	2
	Azithromycin	1
	Daptomycin	1
	Fusidic Acid	1
	Lincomycin	1
	Metronidazole	1
	Rifampicin	1
Anticonvulsants (n = 6)	Lamotrigine	2
	Phenytoin	2
	Valproate	1
	Carbamazepine	1
Antimetabolites (n = 4)	Leflunomide	1
	Methotrexate	1
	Sulfasalazine	1
	Allopurinol	1
Analgesics (n = 2)	Codeine	1
	Codral® (codeine, paracetamol, phenylephrine)	1
NSAIDs (n = 1)	Naproxen	1

Others (n = 9)	Herbal Medications	3
	Amantadine	1
	Amphetamines	1
	Frusemide	1
	Loratidine	1
	Combined oral contraceptive pill	1
	Quetiapine	1