AASLD The Liver Meeting®

CLINICAL OUTCOMES OF IDIOSYNCRATIC DILI ARE IMPROVING IN THE UNITED STATES: RESULTS FROM THE DILIN PROSPECTIVE STUDY, 2004 TO 2024

RJ Fontana [1], PH Hayashi [2], V Chen [1], H Barnhart [3], R Vuppalanchi [4], D Halegoua-DeMarzio [5], V Navarro [5], A Stolz [6], N Chalasani [4], J Gu [3], AS Barritt [7], JH Hoofnagle 8

1. University, of Michigan, Ann Arbor, MI, 2 FDA, Silversprings, MD, 3 Duke Clinical Research Institute, Durham, NC, 4 Indiana University, Indianapolis, IN, 5 Jefferson Medical College, Philadelphia, PA, 6 University of Southern California, Los Angeles, CA, 7 University of North Carolina, Chapel Hill, NC, 8 NIDDK, Bethesda, MD

DILIN Drug Induced Liver Injury Network

INTRODUCTION

- Idiosyncratic DILI is a rare but important cause of liver injury that can be severe or life-threatening [1,2]
- The Drug Induced Liver injury Network (DILIN) has enrolled > 3000 adults and children with DILI attributed to a multitude of drugs and herbals into the ongoing Prospective Registry study since 2004.
- Testing for alternative causes of liver injury, liver pathology review and causality assessment via expert opinion is undertaken at 6 month follow-up

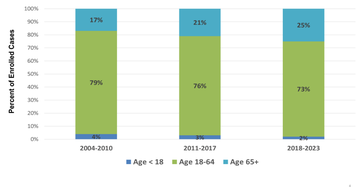
AIM

The aim of this study is to identify temporal changes in the etiology and outcomes of high causality cases enrolled into DILIN from 2004 to 2024

METHODS

- 2627 patients were enrolled between 4/04 and 4/24 including 1983 high causality cases at 9 participating sites (3 legacy)
- Cases were scored as definite (20%), highly likely (52%) or probable (28%).
- Presenting clinical features, suspect drugs, and 6 month outcomes were compared from the 1st (2004-10), 2nd (2011-2017) and 3rd (2018 – 2024) eras using descriptive statistics and trend tests.

DILIN Prospective Registry ('04-24)



RESULTS

Demographics & Presenting features

	'04 -10 (690)	'11-17 (854)	'18- 23 (439)	P trend
Age (yrs)	49.7	52.8	56	< 0.001
Female (%)	59	57	61	0.28
White (%) Black (%) Asian (%) Other (%)	78 12 3 6	78 13 3 5	76 14 5 5	0.41
Latino (%)	11	11.1	10	0.56
BMI (kg/m^2)	26	26.7	26.8	0.15
Diabetes (%)	25	23	19	0.056
Latency (days)	44	44	47	0.87
HIV + (%)	2.6	1.2	0.7	0.019
Chronic liver dz (%)	10	6	6	0.014
Hep/ mix- chol (%)	53/ 22-25	53/ 24-23	57/ 21-22	0.50
Jaundice (%)	71.4	60.7	46	< 0.001
Nausea (%)	60.1	47.5	32.8	< 0.001
Abd pain (%)	43.5	36.2	27.6	<0.001
Fever (%)	28.8	17.3	8.7	< 0.001
Rash (%)	27.8	15.7	10	< 0.001
Itching (%)	53.6	40	25.3	< 0.001
Eo's > 500 (%)	10.8	18.2	17.9	< 0.001
Causality Definite Highly likely Probable	 28 50 22	 17 53 30	 13 53 33	< 0.001

Outcomes and Suspect agents

	'04 -10 (690)	'11-17 (854)	'18- 23 (439)	P trend
Onset ALT (U/l) Onset T. bili (mg/dl)	519 5.0	450 4.7	453 2.9	0.46 < 0.001
Peak ALT (U/l) Peak T. bili (mg/dl) Peak INR	615 9.6 1.2	605 9.4 1.2	610 5.3 1.1	0.84 < 0.001 < 0.001
Steroids (%)	23	21	26	0.17
Mild-mod (%) Mod-hosp (%) Severe (%) Fatal (%)	45 26 21 8	41 37 16 6	50 34 11 5	0.26 0.0016 < 0.001 0.059
Chronic DILI (%)	17	15	14	0.36
Death (%) DILI related (%) Non- DILI (%)	6.7 (60%) (35%)	6.3 (53%) (43%)	5.3 (39%) (62%)	0.53 0.17
Suspect Drugs				
Antimicrobial (%)	46	42	34	<0.001
Anticonvulsant (%)	5	3	2	0.0057
Herbal supplement (%)	15	22	23	<0.001
Antineoplastic (%)	4.6	7.6	17.5	< 0.001
Immune checkpoint (%)	0	2.3%	7.5%	< 0.0001
Individual agents				
Augmentin (%)	10	14	9	0.99
Isoniazid (%)	6	3	1.6	0.0001
Nitrofurantoin (%)	5	3.6	1.8	0.0034
Minocycline (%)	4.1	2.3	1.4	0.0049
Statin (%)	3.2	3.5	4.3	0.60

DILIN Registry from 2004 to 2024

- Median participant age is increasing
- Decreasing proportion with HIV and chronic liver disease may be due to introduction of DAA's for HCV and improved antiretroviral agents for HIV
- Less frequent clinical symptoms at DILI onset and greater eosinophilia may be due to more ICI cases over time.
- Initial and peak liver lab abnormalities decreased over time consistent with less severe liver injury and fewer deaths or transplants
- Fewer cases of antimicrobial, INH, anticonvulsant, nitrofurantoin and minocycline over time
- More cases of herbal and anti-neoplastic DILI likely due to the approval of Immune checkpoint inhibitors in 2010.
- Mini "outbreaks" due to OxyElite Pro ('13-14, n=7), mRNA COVID vaccines ('21-'23, n=18) and French Lentil and Leek crumbles ('22, n=7) were observed [3, 4]

DILI Etiologies by race

	White (78%)	Black (13%)	Asian (4%)	Other (6%)	P
Age (yr)	53	48	51	39	< 0.001
Female (%)	58	66	53	57	0.087
Latency (days)	43	48	52	59	0.33
Hepatocellular (%)	52	55	69	64	0.007
Peak ALT(U/l) Peak Bili (mg/dl)	579 7.6	730 10.9	912 11.2	778 11.3	< 0.001 0.001
Mild-mod (%) Mod-Hosp (%) Severe (%) Fatal (%)	47 32 16 5	34 34 22 10	34 37 18 11	44 35 21 10	< 0.001
Steroids (%)	22	30	18	21	0.025
Chronic (%)	16	22	13	7	0.008
Suspect drugs					
Antimicrobial (%)	42	40	49	38	0.39
Augmentin (%)	13	7.1	1.4	8.5	< 0.001
TMP-SMX (%)	4.3	7.5	8.2	2.6	0.042
Nitrofurantoin (%)	4.4	2.4	0	0.9	0.031
Isoniazid (%)	2.5	5.1	16.4	7.7	< 0.001
Macrolide (%)	2.1	0.8	6.8	0	0.01
Antineoplastic (%) Immune check (%)	10.1 3.1	6.3 2	1.4 0	1.7 0	<0.001 0.078
Herbals (%)	19.4	15.4	26	34.2	< 0.001
Anticonvuls (%)	3.1	7.9	1.4	2.6	0.003

DILI by Race

- White patients are older with lower peak ALT and bilirubin levels and less severe outcomes compared to other groups
- White patients more likely to have amoxicillin/clavulanate, nitrofurantoin, and antineoplastic DILI.
- Black patients more likely to have anticonvulsant DILI which may be genetically mediated.
- Asian patients more likely to have TMP-SMZ, isoniazid, herbal, and macrolide DILI and less likely to have amoxicillin/clavulanate DILI.
- Genetic analyses stratified by subject race are ongoing

CONCLUSIONS

- The median age of DILIN patients is significantly increasing but there is less severe disease at onset and fewer deaths/ transplants.
- There are fewer cases of antimicrobial DILI but more cases of herbal and immune checkpoint inhibitor DILI over time
- Overall clinical outcomes are improving over time with fewer liver-related deaths and transplants possibly due to more ICI cases and earlier recognition of DILI
- Etiologies of DILI significantly vary by race with more amoxicillin/clavulanate, nitrofurantoin, and anti-neoplastic cases in Whites while Blacks tend to have more anti-convulsant DILI and Asians have more herbal DILI.
- Whites were less likely to have severe/ fatal outcomes compared to other racial groups for unclear reasons.

REFERENCES

1 Fontana RJ, et al. Drug induced Liver Injury Network. Drug Safety 2009; 32: 55-68.

2. Chalasani NC, et al. Features and Outcomes of 899 patients with Drug-induced liver injury. Gastroenterology 2015: 148: 1340-1352.

3. Choi G, et al. Characterization of Acute liver injury after ingestion of plant based Food Supplement Aliment Pharmacol 2024 (in press).

4. Fontana RJ, et al. ERAP-1 and ERAP-2 variants in liver injury following COVID-19 mRNA vaccination a US Multicenter study. Am J Gastroenterol 2024; 119; 1496-1505.

ACKNOWLEDGEMENTS

Research supported by the NIDDK via U01-DK065184 (University of Michigan), U01-DK065201 (UNC), U01-DK-65211 (Indiana), U01-DK083020 (USC), U01-DK083027 (Jefferson), and U24-DK065176 (DCRI).

CONTACT INFORMATION

Robert J. Fontana, MD

rfontana@med.umich.edu

For further information see https://dilin.org