

Background

- Alcohol use disorder (AUD) and its complications are increasing globally.
- Medications for alcohol use disorder (MAUD) can improve survival, however, concerns about drug-induced liver injury (DILI) often deter physicians from prescribing MAUD.
- We aim to explore DILI due to MAUD enrolled in the US Drug Induced Liver Injury Network (DILIN) and their HLA association.

Methods

- High confidence cases (definite, highly likely, or probable) of DILI due to MAUD enrolled into the DILIN prospective study from 2004 to 2024 were reviewed.
- HLA allele frequency (AF) of disulfiram DILI cases (n=9) was compared to 456 matched non-disulfiram DILI controls from the DILIN (DILI controls) to assess HLA association.

Results

Patients enrolled in DILIN prospective study between September 2004 to March 2024 (n=2622)

Patients underwent formal adjudication (n=2495)

Patients scored as definite, highly likely or probable DILI (n=1975)

DILI due to Disulfiram (n=11)

DILI due to Naltrexone (n=1)

DILI due to Baclofen (n=1)

Results

Table 1. Baseline characteristics of patients with DILI due to MAUD

Characteristic	Disulfiram (n=11)	Baclofen (n=1)	Naltrexone (n=1)
Age (years)	43.8 (31.5, 61.3)	61	59.7
Gender, Female	8 (72.7%)	1 (100.0%)	1 (100.0%)
Self reported race			
Caucasian	9 (81.8%)	1 (100.0%)	1 (100.0%)
Asian	2 (18.2%)		
Hispanic	1 (9.1%)		
Body mass index (kg/m ²)	24.3 (19.5,33.8)	27.8	22.3
Diabetes mellitus	1 (9.1%)	-	-
Prior drug allergies	5 (45.5%)	-	-
Duration of therapy (days)	32 (11,74)	117	6
Diagnostic serologies			
ANA or SMA positive	4 (36.4%)	1 (100.0%)	-
Eosinophilia(> 500/μL)	3 (30%)	-	-
R value at onset	27.9 (7.6,72.5)	19.3	13.3

Data presented as median (range). Abbreviations : ANA – anti-nuclear antibody; SMA – smooth muscle antibody

Table 2. Selected characteristics and outcome of patients with DILI due to MAUD

Drug	Age / Sex	Prior liver disease	Latency (days)	Peak ALT (U/L)	Peak ALP (U/L)	Peak T Bili (mg/dL)	Causality score	DILIN severity score	Outcomes
Disulfiram	34/M		24	2467	176	1.7	Highly likely	Mild	Recovery
Disulfiram	44/F		20	6698	444	13.6	Definite	Moderate-hospitalized	Recovery
Disulfiram	44/F	ALD	35	1365	286	20	Definite	Severe	Treated with steroid
Disulfiram	46/F		63	2670	381	28.4	Definite	Fatal	Underwent liver transplant
Disulfiram	42/M	HCV	34	1715	137	5.9	Highly likely	Moderate-hospitalized	Recovery
Disulfiram	57/F	Cirrhosis due to ALD	67	4691	251	34	Highly likely	Severe	Treated with steroid
Disulfiram	45/M		46	1286	244	30.6	Definite	Severe	Recovery
Disulfiram	31/F	ALD	52	2516	357	18.6	Highly likely	Fatal	Underwent liver transplant
Disulfiram	44/F		21	1060	87	0.3	Highly likely	Mild	Recovery
Disulfiram	50/F	ALD	28	5320	232	4.9	Highly likely	Severe	Recovery
Disulfiram	61/F	Cirrhosis due to ALD	12	3220	226	16	Probable	Fatal	Liver related death
Naltrexone	59/F		8	730	126	0.7	Probable	Mild	Recovery
Baclofen	61/F		112	1446	129	2.6	Probable	Moderate-hospitalized	Recovery

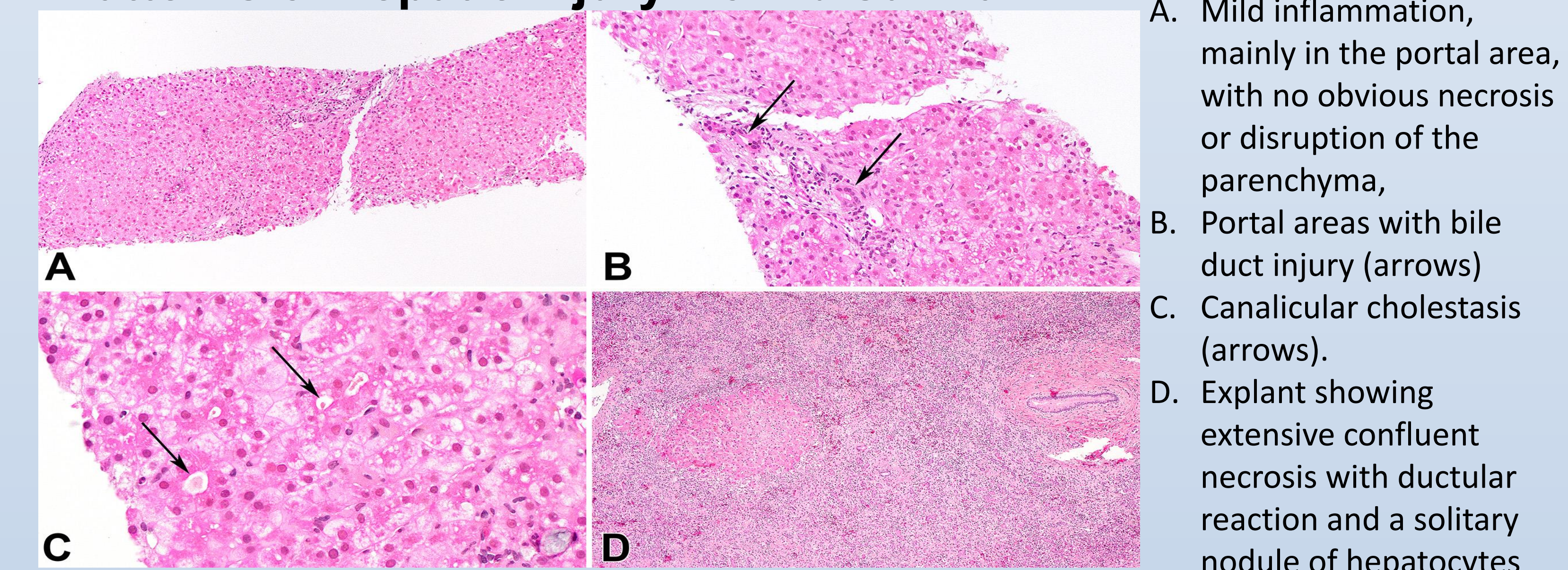
Abbreviations: ALT-Alanine aminotransferase; ALP- Alkaline phosphatase; ALD: alcohol associated liver disease

Table 3. HLA alleles associated with risk of disulfiram-DILI

Allele	Disulfiram-DILI (n=9)		Non-disulfiram DILI controls (n=456)		OR (95% CI)	p value
	AF	CF	AF	CF		
C*01:02	0.167	0.333	0.031	0.059	6.29 (1.10, 24.1)	0.020
DRB1*09:01	0.111	0.222	0.012	0.024	10.16 (1.01, 52.7)	0.024

Abbreviations : AF – allele frequency; CF – Carriage frequency; OR – Odds ratio

Patterns of hepatic injury from disulfiram



- A. Mild inflammation, mainly in the portal area, with no obvious necrosis or disruption of the parenchyma,
- B. Portal areas with bile duct injury (arrows)
- C. Canaliculal cholestasis (arrows).
- D. Explant showing extensive confluent necrosis with ductular reaction and a solitary nodule of hepatocytes

Conclusion

- Disulfiram is the leading cause of DILI among MAUD and is most frequently encountered in women and is associated with significant fatality/transplant rate.
- Disulfiram DILI is associated with HLA-C*01:02 and DRB1*09:01. Baclofen and naltrexone can cause mild to moderate self-limited DILI.
- However, there were no cases of acamprosate DILI.
- These findings demonstrate the generally favorable safety profile of MAUD other than disulfiram.

Acknowledgement

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