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Hormonal Contraceptive-Associated Liver Injury in the Modern Era - Insights from the Drug-Induced Liver Injury Network

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DILIN Drug-Induced Liver Injury Network

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INTRODUCTION

Earlier high-estrogen oral contraceptives (OCs) were linked to cholestatic drug-induced liver injury (DILI) with jaundice and pruritus, resolving after discontinuation. Although newer low-dose formulations show fewer liver enzyme elevations, isolated reports continue to raise hepatic safety concerns.

AIM

The U.S. Drug-Induced Liver Injury Network (DILIN) enables systematic capture of rare idiosyncratic DILI cases. This analysis examined DILI associated with hormonal agents used for contraception or dysfunctional uterine bleeding, detailing implicated drugs, clinical and biochemical features, liver histology, and outcomes.

METHODS

DILIN is a multi-center network of 5 to 8 U.S. medical centers funded by the NIH that identify and enroll cases of suspected idiosyncratic DILI (NCT00345930). This study selected cases with high confidence of DILI (causality scores 1 to 3) to examine the demographic, clinical, biochemical, and histologic characteristics and identify signature patterns. Female DILI cases from the DILIN database who were not treated with hormonal agents and had adjudication scores of high confidence and body mass index of ±5 kg/m^2 were selected as controls. For identifying genetic risk variants for hormonal-agent DILI, we targeted a list of known cholestasis-related genes. A total of 82 genes were assessed. Variants located within each gene region, including a ±10 kb boundary, were analyzed. Fisher's exact tests were performed to test the genetic association with DILI due to hormonal agents.

RESULTS

Table 1. Select demographics and clinical features

Feature*	Hormonal agent (N=20)	Control (N=60)	P-value
Age (years), median (Q1, Q3)	22.1 (18.3, 29.4)	22.1 (18.3, 29.4)	0.96
Female Sex	100%	100%	NC
Race			
White	15/20(75%)	48/60(80%)	0.384
Black	3/20 (15%)	6/60(10%)	
Asian	0/20	4/60 (6.7%)	
Other	2/20	3/60(3.3%)	
Hispanic	2/20 (10%)	6/60(10%)	>0.999
BMI (kg/m^2)	26.8 (7.8)	25.1 (6.4)	0.78
History of Drug Allergies	4/20(20%)	18/60 (30%)	0.39
Alcohol use (any)	5/20 (25%)	25/56 (44.6%)	0.123
Drug start to the onset of DILI (days)			
• Median (Q1, Q3)	35.5 (26.0, 71.5)	59.5 (26.5, 163.0)	0.334
• Mean (SD)	107.0 (168.92)	170.7 (309.94)	
➢ <= 1 week	0/20	3/60 (5.0%)	0.532
➢ 2 to 4 weeks	6/20 (30.0%)	13/60 (21.7%)	
➢ 5 to 12 weeks	10/20 (50.0%)	21/60 (35.0%)	
➢ 13 to 24 weeks	1/20 (5.0%)	8/60 (13.3%)	
➢ > 24 weeks	3/20 (15.0%)	15/60 (25.0%)	
Causality Score			
Definite	5/20 (25.0%)	18/60 (30.0%)	0.912
Highly Likely	11/20 (55/0%)	31/60 (51.7%)	
Probable	4/20 (20.0%)	11/60 (18.3%)	
Symptoms			
• Jaundice	16/20 (80.0%)	29/60 (48.3%)	0.013
• Nausea	8/20 (40.0%)	35/60 (58.3%)	0.154
• Fever	0/20	21/60 (35.0%)	0.002
• Abdominal pain	5/20 (25.0%)	35/60 (58.3%)	0.010
• Rash	3/20 (15.0%)	19/60 (31.7%)	0.148
• Itching	16/20 (80.0%)	23/60 (38.3%)	0.001

Table 2. Biochemical features of cases of DILI

Feature*	Hormonal agent (N=20)	Control (N=60)	P-value
Initial ALT (U/L)	353 (337)	952 (969)	0.001
Initial AST (U/L)	187 (183)	772 (846)	<0.001
Initial ALP (U/L)	213 (157)	196 (160)	0.324
Initial Total Bilirubin (mg/dL)	7.5 (5.5)	3.9 (4.4)	0.003
Initial R value	5.0 (5.8)	16.0 (20.4)	<0.001
Enzyme Pattern			0.003
Hepatocellular (R ≥ 5)	5/18 (27.8%)	40/57 (70.2%)	
Mixed (R >2 to <5)	6/18 (33.3%)	11/57 (19.3%)	
Cholestatic (R ≤ 2)	7/18 (38.9%)	6/57 (10.5%)	
Peak ALT (U/L)	504 (397)	1311 (1379)	<0.001
Peak AST (U/L)	326 (458)	1308 (1894)	<0.001
Peak ALP (U/L)	280 (176)	269 (229)	0.386
Peak Total Bilirubin (mg/dL)	13.0 (9.18)	8.4 (9.78)	
Peak INR	1.2 (0.51)	1.6 (1.58)	
Peak Eosinophils (cells/µL)	203.1 (216.40)	401.7 (794.44)	0.193
Peak Eosinophils >500 cells/µL	1/20 (5.0%)	10/57 (17.5%)	0.271
ANA	2/20 (10.0%)	28/58 (48.3%)	0.002
SMA	4/17 (23.5%)	12/56 (21.4%)	0.013
Severity Assessment			0.088
Mild (Anicteric)	4/20 (20.0%)	23/60 (38.3%)	
Moderate (Jaundiced)	5/20 (25.0%)	8/60 (13.3%)	
Moderate & Hospitalized	10/20 (50.0%)	15/60 (25.0%)	
Severe (Decompensation)	1/20 (5.0%)	11/60 (18.3%)	
Fatal (Death or Transplant)	0/20	3/60 (5.0%)	
Liver Biopsy	10/20 (50%)	26/60(43.3%)	0.604
Hospitalization	9/20 (45.0%)	41/60 (68.3%)	0.062
Treated with corticosteroids	3/20 (15.0%)	21/60 (35.0%)	0.091
Chronic DILI	2/19 (10.5%)	8/52 (15.4%)	0.719
Death or Liver Transplant	0	0	

Table 3. Top genetic variants reaching P-value ≤ 0.005

Chr:BP	SNP	Gene	Location	Allele	Case AF	Control AF	OR (95% CI)	P-value
2:233780897	rs6722064	*MROH2A*	intronic	G	0.55	0.25	3.58 (1.67, 7.65)	0.001
7:138115259	rs34315519	*AKR1D1*	intronic	A	0.18	0.44	0.28 (0.11, 0.68)	0.004
2:43871716	rs3795860	*ABCG8*	intronic	C	0.23	0.48	0.31 (0.14, 0.71)	0.005
2:110177146	rs1154652	*NPHP1*	Intronic	G	0.35	0.14	3.41 (1.46, 7.96)	0.005
9:69254557	rs3812536	*TJP2*	UTR3	A	0.68	0.42	3.01 (1.36, 6.66)	0.007
12:100559789	s35728	*NR1H4*	Intronic	A	0.63	0.37	2.89 (1.34, 6.25)	0.008

Abbreviation: Chr:BP – chromosome and basepair; **SNP:** single nucleotide polymorphism; **AF:** allele frequency; **OR (95% CI):** odds ratio (95% confidence interval)

- The median age of women (15 White, 3 Black, 2 Other) was 22.1 years, with a latency of 2–12 weeks, and most presented with jaundice and pruritus.
- Fourteen cases received a combination of HC, three were estrogen-only, and one case received progesterone-only.
- The injury was mainly cholestatic or mixed, with 50% requiring liver biopsy or hospitalization.
- One patient who received (intravenous Premarin followed by oral estradiol) experienced prolonged jaundice with vanishing bile duct syndrome, but there were no fatalities or liver transplantation. Chronic DILI was seen in 10.5% of cases.
- We did not find any HLA variants meeting the significant threshold.
- *MROH2A, NR1H4, NPHP1*, and *TJP2* showed increasing the risk of DILI (OR > 1).
- *ABCG8* and *AKR1D1* showed protective effect on decreasing the risk of DILI.

CONCLUSIONS

- **Hormonal agent-induced liver injury presents with unique** cholestatic phenotype, often lacking the inflammatory features.
- ***MROH2A* gene ranks as the top potential candidate variant to increase the risk of hormonal agent-induced DILI (OR (95% CI)=3.58 (1.67, 7.65), p=0.001).**

CONTACT INFORMATION

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