Drug-Induced Liver Injury [DILI] Ascribed to Non-Steroidal Anti-Inflammatory Drugs [NSAIDs] in the USA—an Update with Genetic Correlations from the US Drug-Induced Liver Injury Network [DILIN]

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Drug-Induced Liver Injury Network

Introduction

NSAIDs are widely used throughout the world, mainly for management of chronic inflammatory and painful conditions. NSAIDs rarely cause idiosyncratic, non-dose dependent liver injury. Recent evidence from the US DILIN, as well as elsewhere, implicates host immune responses as central to pathogenesis of such idiosyncratic DILI. Previously, we reported the US DILIN experience with NSAID DILI for 2004-2013 [Liv Intl 36:603-09].

Aims

To update our clinical experience and report on HLA and other genetic factors recently described as important in idiosyncratic DILI.

Methods

- **The US DILIN,** begun in 2004; is comprised of clinical sites [currently 7 in number], a data coordinating center, and the NIDDK. We enroll subjects with suspected DILI and follow them for at least 6 months. We adjudicate causality both with RUCAM, and RECAM and by a Delphic approach and grade severity from mild to fatal or requiring liver transplant.
- **Liver histopathology:** Available liver biopsies were sent to and reviewed by a single expert liver histopathologist (DEK). The biopsies were scored for multiple histological features as well as an overall pattern of liver injury.
- **Statistical analysis:** Cohorts were described with summary statistics such as medians with (interquartile ranges) for continuous variables and frequencies with percent for categorical variables. Comparisons between the confirmed NSAID DILI cases and the confirmed non-NSAID DILI drug cases were compared by two sample Wilcoxon tests for continuous variables and by chi-square tests for categorical data.
- **Ancestry analysis:** The genetic ancestry of each case and control was inferred by EIGENSTRAT. We identified 33 cases and 17,842 controls of European-American (EA) origin, 8 cases and 5,816 controls of African-American (AA) origin, and 8 cases and 2,919 controls of Hispanic origin (HSP). In the combined sets of cases and controls of each ancestry, principal component (PC) analysis was performed to estimate PCs, which were modeled in the association analysis as covariates to correct for ancestral backgrounds.
- **HLA allele sequencing** HLA alleles of 52 NSAID cases and 1332 DILI cases due to non-NSAID prescription drugs were determined using sequencing by Illumina MiSeq.

Results

- Between Sep 2004 and Mar 2022, we enrolled 2,626 subjects and adjudicated causality at 6 months in 2,498. Following adjudication, we identified 55 [41 (75%) women] as definitely [>95%], highly likely [75-95%], or probably [51-74% likely] due to NSAIDs.
- **Fig 1.– Summary Flow Diagram of Subjects Studied.** Total numbers of subjects studied between September 2004 and March 2022 are shown with the numbers of subjects previously described (studied between September 2004 and August 2013 shown in parentheses).

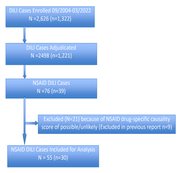


Table 1--Selected clinical, demographic, and laboratory features of NSAID DILI subjects [2004-2022] vs DILI due to other OTC or Prescription Drugs.

Feature	Total N= 1570	NSAID N = 55	Non-NSAID Drug N= 1515	p value
Age [years]	53.8 40.7, 64.2	55.2 44.8, 64.4	53.7 40.5, 64.2	0.2
Female gender	956/1570 60.9%	41/55 74.5%	915/1515 60.4%	0.035
Body mass index [kg/m²]	26.4 23.2,30.7	28.6 24.9, 34.2	26.3 23.1, 30.6	0.004
Latency [days]	41 10, 70	51 17, 90	41 9, 69	0.47
Laboratory Studies at Onset				
Serum ALT [U/L]	450 242, 929	708 360,1419	442 240,910	0.002
Serum AST [U/L]	300 147, 791	484 217, 1155	293 145, 772	0.007
Serum AP [U/L]	225 145, 360	197 123, 297	227 146, 362	0.128
Serum total bilirubin [mg/dL]	4.2 1.1, 8.1	3.8 0.9, 12.5	4.2 1.1, 8.0	0.529
BUN at onset [mg/dL]	13.0 9, 18	15.0 8, 17	13 9, 18.5	0.890
Serum creatinine [mg/dL]	0.8 0.7, 1.1	0.9 0.7,1.1	0.8 0.7, 1.0	0.569
International Normalized Ratio	1.1 1.0, 1.4	1.2 1.0, 1.4	1.1 1.0, 1.4	0.924
Antinuclear antibody positive	433/1447 29.9%	13/52 25%	420/1395 30.1%	0.43
Smooth muscle antibody positive	327/1395 23.4%	11/51 21.6%	316.1344 23.5%	0.75
R at onset	5.2 2.1, 14.2	10.4 4.3, 21.4	5.1 2.0, 13.8	<0.001
MELD at onset	16 11, 20	17 12, 20	16 11, 20	0.58
Liver Biopsy Done	715/1570 45.5%	31/55 56.4%	684/1511 45.1%	0.10
Treatment with corticosteroids	393/1567 25.1%	16/55 29.1%	377/1512 24.9%	0.48
Outcomes				
Death	104/1390 7.5%	4/53 7.5%	100/1337 7.5%	> 0.999
Liver Transplant	57/1570 3.6%	2/55 3.6%	55/1515 3.6%	> 0.999
Chronic DILI	222/1346 16.5%	9/48 18.8%	213/1298 16.4%	0.67

Table 2-Drugs Implicated in Causing NSAID DILI in the Drug-Induced Liver Injury Network Study, 2004-2022.

Drug	Early Cohort [Sep 2004-Aug 2013] [n = 30]	Subsequent Cohort [Sep 2013-Mar 2022] [n= 25]	Total Cohort [Sep 2004-Mar 2022] [n = 55]	No. of Cases/1 million Rx written in USA, 2019$^{\delta}$	No. of Cases/1 million patients prescribed in 2019$^{\delta}$
Diclofenac [+/- misoprostol]	16*	13#	29^	2.87	7.19
Celecoxib	3	4	7	1.06	3.68
Ibuprofen [+/- famotidine]	2	3	5	0.23	0.45
Etodolac	2	2	4	5.62	12.27
Meloxicam	3	1	4	0.19	0.62
Oxaprozin	2	0	2	N/A	N/A
Naproxen@	0	1	1	0.085	0.22
Nimesulide	0	1	1	N/A	N/A
Sulindac	1	0	1	3.13	8.77
Valdecoxib	1	0	1	N/A	N/A

Table 3. Summary of Histological Features in 13 Subjects with DILI due to NSAIDs who Underwent Liver Biopsies

Subject #	Drug	Ishak Inflam Score	PICs/Eos	Necrosis	Cholestasis	Duct Injury	Duct Loss	AIH-like	Pattern
1	Celecoxib	4	-/+	0	++	Yes	0	No	Cholestatic hepatitis
2	Celecoxib	4	-/-	0	0	Yes	0	No	Chronic cholestasis
3	Celecoxib	5	-/-	0	++	Yes	Moderate	No	Cholestatic hepatitis, VBDS
4	Celecoxib	8	-/+	0	0	Yes	0	No	Chronic hepatitis
5	Diclofenac	17	-/-	++++	+	No	0	No	Acute hepatitis with necrosis
6	Diclofenac	11	-/+	++	0	Yes	0	Yes	Acute hepatitis with necrosis
7	Diclofenac	8	-/-	+	0	No	0	No	Zone 3 necrosis
8	Diclofenac	15	-/-	++++	0	No	0	No	Acute hepatitis with necrosis
9	Diclofenac	15	-/-	0	+	No	0	Yes	Acute hepatitis
10	Ibuprofen	10	-/+	0	0	Yes	0	No	Acute hepatitis
11	Ibuprofen	10	-/+	0	0	No	0	No	Acute hepatitis
12	Naproxen	13	-/-	+	0	Yes	0	No	Acute hepatitis

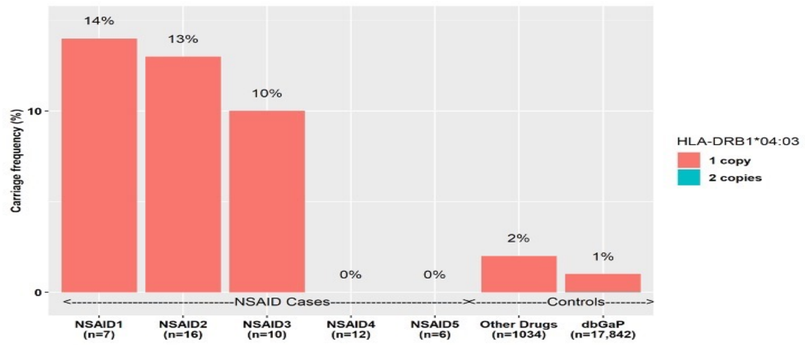
Abbreviations Used: AIH, auto-immune hepatitis; Eos, eosinophils; Inflam, inflammation; PIC, plasma cells; VBDS: Vanishing bile duct syndrome

Results

Table 4-- Summary Association of the most Associated HLA Alleles across Ethnicities

Group	HLA allele	OR (95%CI)	P	Case AF	Ctrl AF	Pop AF	CR cases
EA cohort (n = 33)	DRB1*04:03	14.82 (4.79-36.96)	0.0001	0.06	0.005	0.006	12
	B*35:03	5.11 (1.89-11.17)	0.0030	0.08	0.02	0.02	15
Hispanic cohort (n = 8)	DRB1*04:03	64.8 (7.35-571.4)	0.02	0.06	0.001	0.02	13
	B*35:03	7.65 (1.72-34.08)	0.03	0.13	0.02	0.01	25
AA cohort (n = 8)	DRB1*04:03	13.3 (1.73-102.4)		0.06	0.0050	0.002	13
	B*35:03			-		0.003	
	B*57:03	6.03 (1.71-21.23)	0.0198	0.18			38
EA Diclofenac cohort (n =17)	DRB1*04:03	12.26 (2.92-51.54)	0.0132	0.06	0.0051	0.006	12
	B*35:03					0.02	

Fig.2-- Frequencies of HLA-DRB1:04:03 in the European-American NSAID-DILI cases by Causality Likelihood Scores [NSAID1-5] and Compared to Other Drugs and Population Controls



*Note the significantly increased frequencies of DRB1*04:03*
And higher likelihood of this HLA in high confidence NSAID DILI cases v others.

Conclusions

- NSAID DILI is relatively rare in the US. The most common cause is diclofenac, which, if prescribed, should carry with it special warnings of risk and close observation, as in the package insert.
- Risks are also high for etodolac and sulindac.
- There are typical and differing 'signatures' of DILI for different drugs: specifically, drugs that lead to more cholestatic-types of liver injury, namely, celecoxib, meloxicam, or oxaprozin [R* values of 2.5, 1.3, and 5.4, respectively] also have shorter latencies [31, 22.5, and 16 days, respectively].
- The increased frequencies of *HLA DRB1*04:03*, an HLA type known to be associated with auto-immune disorders, suggests that there are innate host genetic factors that modulate susceptibility and that immune-mediated responses are of central importance in pathogenesis.
- *[*R =ALT/ULN ALT divided by AP/ULN AP]*

https://dilin.dcri.duke.edu

Study supported by NIDDK, NIH. See DILIN website https://dilin.dcri.duke.edu/publications-1 for a complete listing of funding sources, sites, investigators, co-investigators, coordinators, and staff.

***see abstract book for full disclosures**