



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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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=65	NSAID Drug N=55	Non-NSAID Drug N=10	p value
Age (years)	53.8	55.2	53.7	0.2
Female gender	60/1570	41/85	9/19	0.05
Body mass index [kg/m ²]	25.4	25.9	25.3	0.004
Latency (days)	23.2, 30.7	51	41	0.47
	15, 20	17, 30	5, 6	
Laboratory Studies at Onset				
Serum ALT [U/L]	450	701	442	0.002
Serum AST [U/L]	242, 809	390, 1419	249, 810	
Serum AP [U/L]	300	484	293	0.001
Serum ALP [U/L]	142, 791	217, 1055	145, 772	0.128
Serum total bilirubin [mg/dL]	2.2	1.3, 2.97	1.45, 3.92	0.523
BUN at onset [mg/dL]	1.1, 1.1	0.9, 12.5	1.1, 8.0	0.890
Serum creatinine [mg/dL]	0.8	0.9	0.8	0.565
International Normalized Ratio	1.1	1.2	1.1	0.924
Antinuclear antibody positive	1.0, 1.4	1.0, 1.4	1.0, 1.4	0.43
Smooth muscle antibody positive	433/1447	293	420/1395	0.75
R at onset	23.4%	21.6%	23.9%	0.901
MELD at onset	1.1	1.2	1.1	0.58
Liver Biopsy Done	11, 20	13, 20	6, 10	0.10
Treatment with corticosteroids	15/1570	31/55	6/10	0.48
Outcomes				
Death	104/1390	4/5	100/137	> 0.999
Liver Transplant	57/1570	2/5	55/1515	> 0.999
Discharge	32/1570	4/5	28/137	0.07

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*	No. of Cases/1 million patients prescribed in 2019*
Diclofenac [+/- misoprostol]	16*	13*	29*	2.87	7.19
Celecoxib	3	4	7	1.06	3.68
Ibuprofen [+/- farnesitidine]	2	3	5	0.23	0.45
Etoricoxib	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	0.85	0.22
Nimesulide	0	1	1	N/A	N/A
Sulindac	1	0	1	3.14	3.77
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	Acute hepatitis Eos	PIC/Eos	Necrosis	Cholestasis	Duct injury	Duct Loss	AH/HS	Pattern
1	Celecoxib	+	-	+	+	+	+	+	Cholestatic hepatitis
2	Celecoxib	+	-	+	+	+	+	+	Cholestatic hepatitis
3	Celecoxib	+	-	+	+	+	+	+	Cholestatic hepatitis
4	Celecoxib	+	-	+	+	+	+	+	Cholestatic hepatitis
5	Celecoxib	+	-	+	+	+	+	+	Cholestatic hepatitis
6	Diclofenac	+	-	+	+	+	+	+	Acute hepatitis with cholestatic features
7	Diclofenac	+	-	+	+	+	+	+	Acute hepatitis with cholestatic features
8	Diclofenac	+	-	+	+	+	+	+	Cholestatic hepatitis
9	Diclofenac	+	-	+	+	+	+	+	Acute hepatitis with cholestatic features
10	Diclofenac	+	-	+	+	+	+	+	Acute hepatitis
11	Naproxen	+	-	+	+	+	+	+	Acute hepatitis
12	Naproxen	+	-	+	+	+	+	+	Acute hepatitis

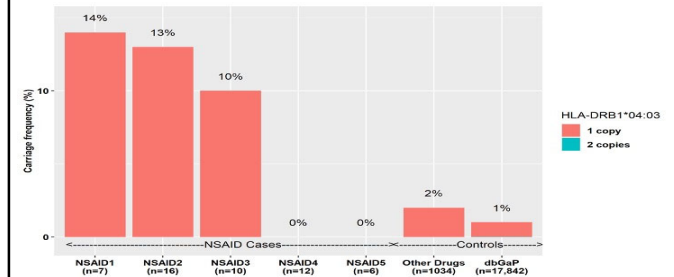
Abbreviations Used: AH, auto-immune hepatitis; Eos, eosinophils; Inflamm, inflammation; PIC, plasma cells; VBDS: Vanishing bile duct syndrome

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	
EA Diclofenac cohort (n = 17)	B*57:03	6.03 (1.71-21.23)	0.0198	0.18			38
	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 [NSAID-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://diln.dcri.duke.edu>

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***see abstract book for full disclosures**