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Dose-Dependent Hypersensitivity-Type DILI

A Case Series

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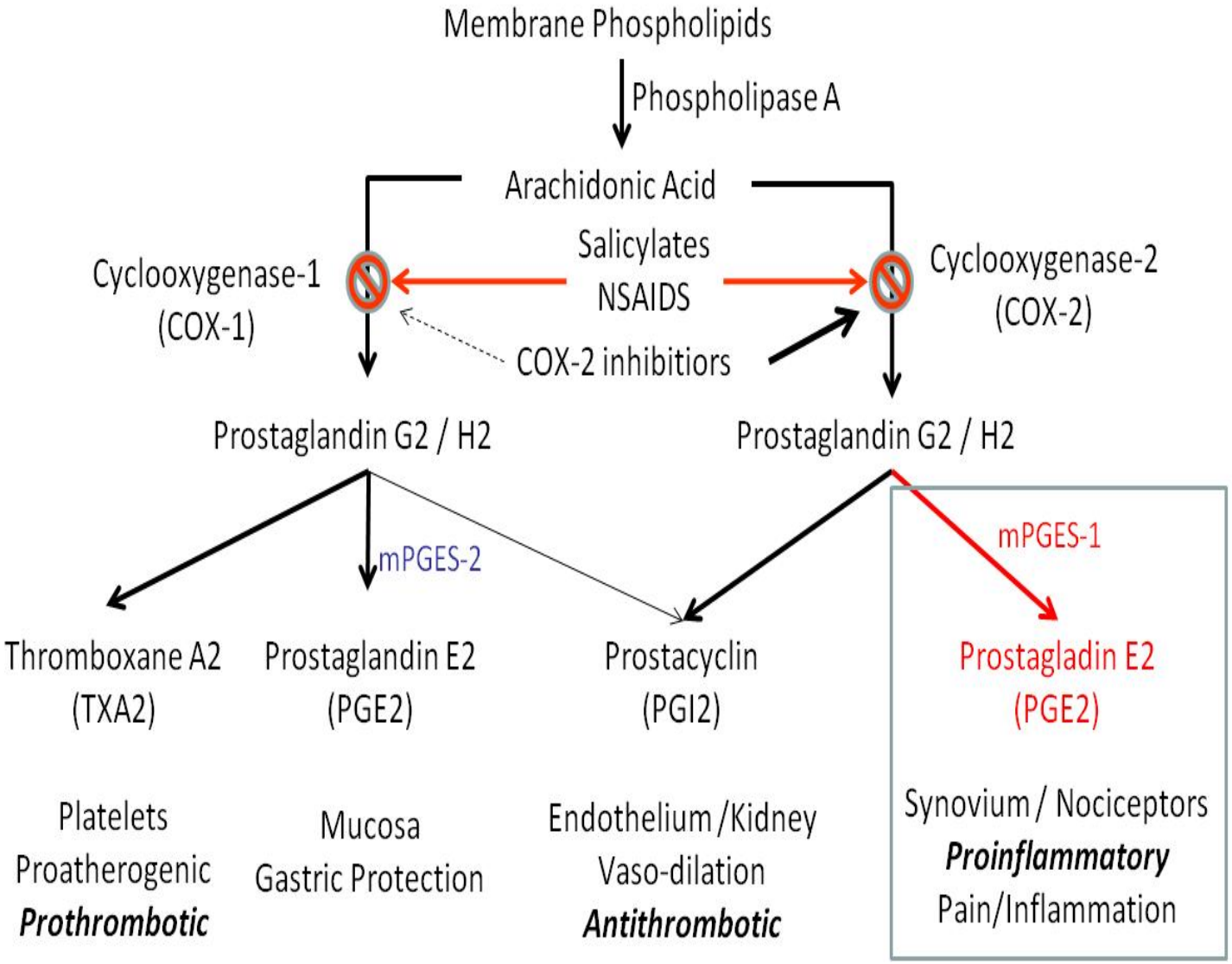
Background

- Mechanisms underlying idiosyncratic DILI are still a matter of debate
- Both metabolic and immune-mediated DILI mechanisms are still not completely understood
- Although allergic/ hypersensitivity-type idiosyncratic DILI is seen more often with drugs given in higher daily doses (usually >50 mg/day), a dose-response relationship has rarely been described for individual drugs
- This case series describes 6 patients that presented with acute hepatocellular DILI with hypersensitivity features during a Phase I clinical trial with a novel anti-inflammatory drug

Microsomal Prostaglandin E Synthase-1 (mPGES-1) Inhibitors as Treatment of Pain and Inflammation



Study Design

- Phase I clinical trial with healthy volunteers
- Subject/investigator blind, parallel-group, multiple-dose, dose-escalation study, 28 days duration
- Hepatic biochemical tests done at least once weekly
- 5 treatment groups:

Treatment	Dose	Treated Subjects
Placebo	-	6
Comparator NSAID*	400 mg	6
LY	25 mg	8
LY	75 mg	10
LY	225 mg	9

*Celecoxib 400mg once daily

Study Design and Outcome

- A priori-defined discontinuation criteria were used to guide withdrawal of individual subjects from the study or discontinue dose escalation
- Subjects with liver disease or heavy alcohol users were excluded
- Plasma and urine were qualitatively analyzed using Liquid Chromatography/ High Resolution Mass spectrometry (HPLC/HRMS) to determine preliminary metabolic profile, assess reactive metabolite formation
- The trial was terminated early after 2 cases of DILI were discovered in subjects who received 225 mg of LY for about 19 days
- After LY administration was discontinued, 4 more cases of DILI were identified
- All 6 subjects recovered following discontinuation of LY

Clinical Presentation of DILI Cases

#	Age (yrs)	M/F	Dose (mg)	Day of Presentation After Drug Initiation	Rash	Max ALT (xULN)	Max ALP (xULN)	Max TBL (mg/dL) (NR: 0-1.2 mg/dL)	Max Eos (%) (NR: 0-6%)
1	53	M	75	34	Yes	3.3	0.7	1.5	6
2	58	F	225	17	No	27.3	1.5	1.2	20
3	32	M	225	33	Yes*	5.8	0.6	1.2	10
4	57	F	225	16	No	14.9	0.7	1.0	19
5	59	F	225	16	No	19.2	1.1	0.8	14
6	54	F	225	17	Yes*	45.6	1.2	1.6	21

- 4 females, 2 males, ages 32-59
- Normal hepatic biochemical tests at baseline
- Presentation 16-34 days (mean 22 days) after starting study drug
- Symptoms included epigastric pain, fatigue, nausea, low-grade fever, rash

*Urticaria

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- ALT levels >3X ULN in all 6 cases, ≥15X ULN in 4, >45X ULN in 1
- ALP and total bilirubin did not exceed 1.5X ULN
- Eosinophilia of >10% in 5 subjects, > 20% in 2
- Viral serology was negative for hepatitis A,B,C,E in all 6 subjects
- Autoimmune serology including ANA, ASMA was negative in all 6 subjects
- Abdominal ultrasonography was normal in all 6 subjects

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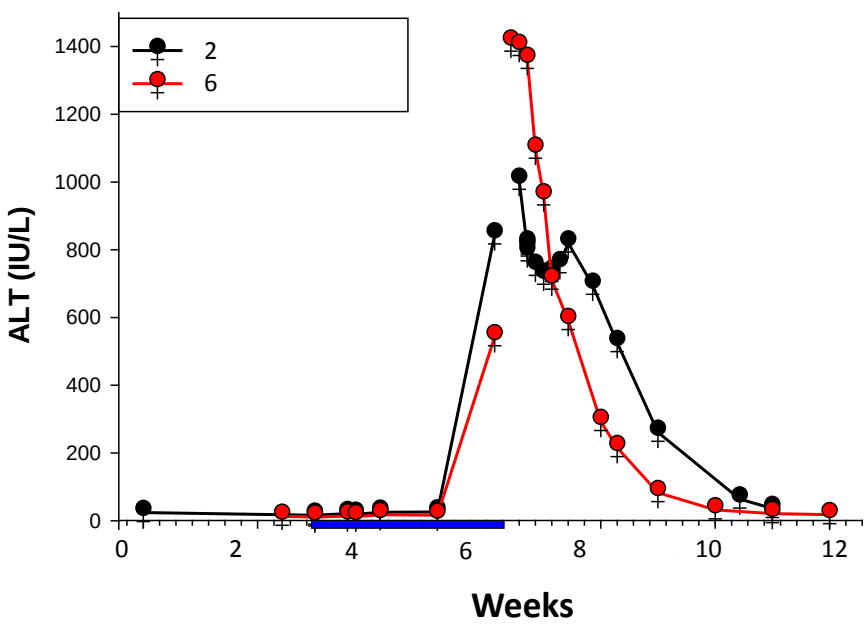
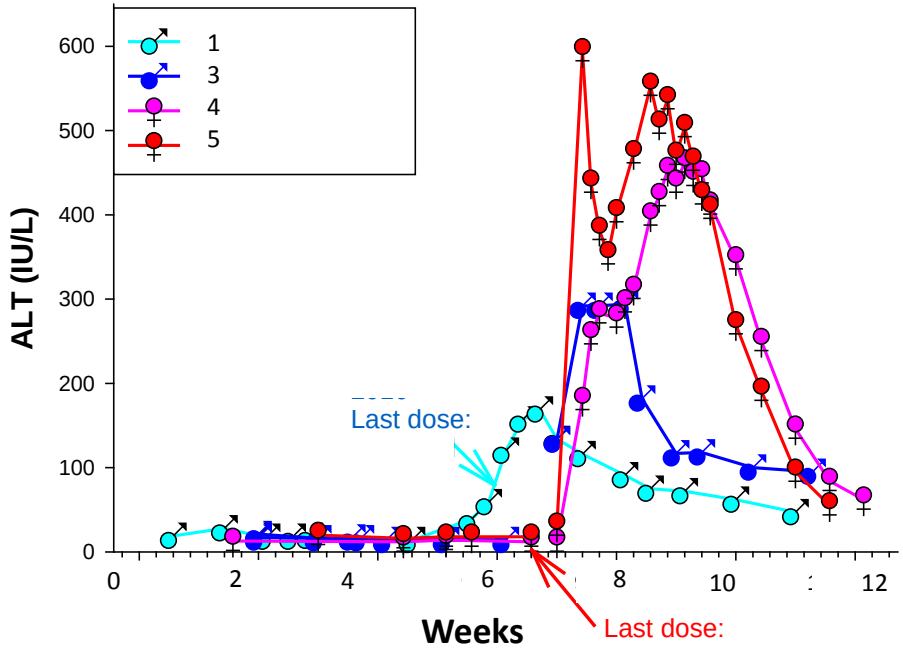
Clinical Course

- Two patients required hospitalization, and were treated by local hepatologists with N-acetylcysteine
- Both underwent liver biopsy*
- ALT returned to normal range within 6-10 weeks after drug discontinuation

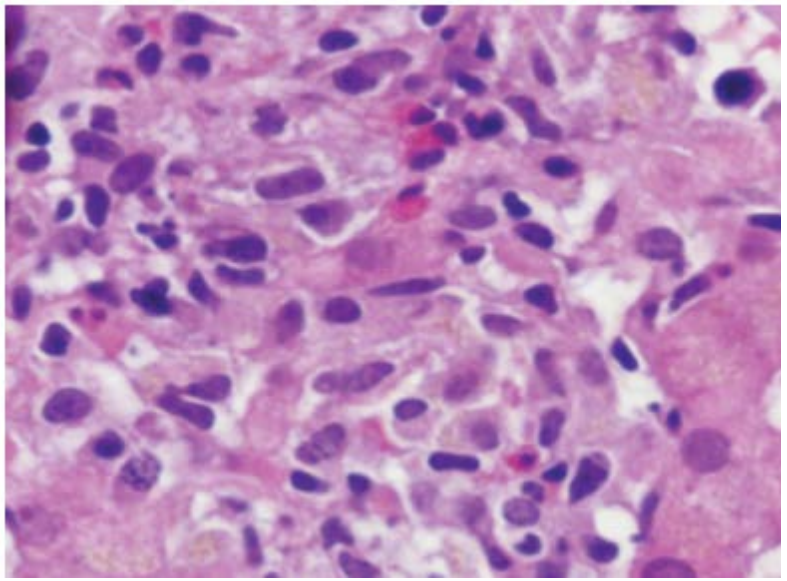
*Marumoto A, et al. Hawai'i Journal of Medicine & Public Health 2013;72(9)Supp4:30-33

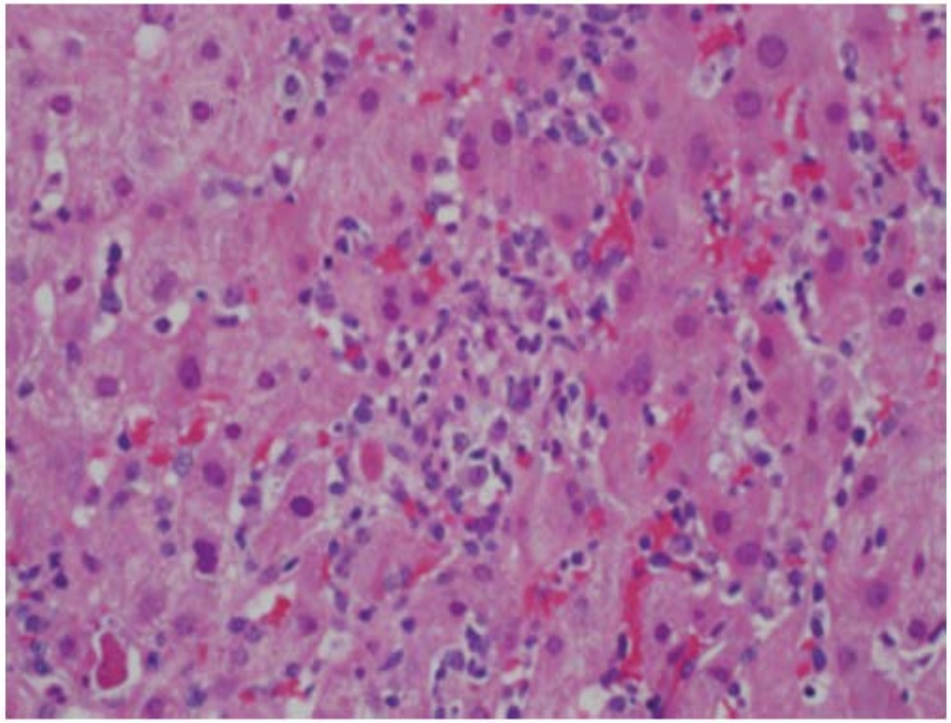


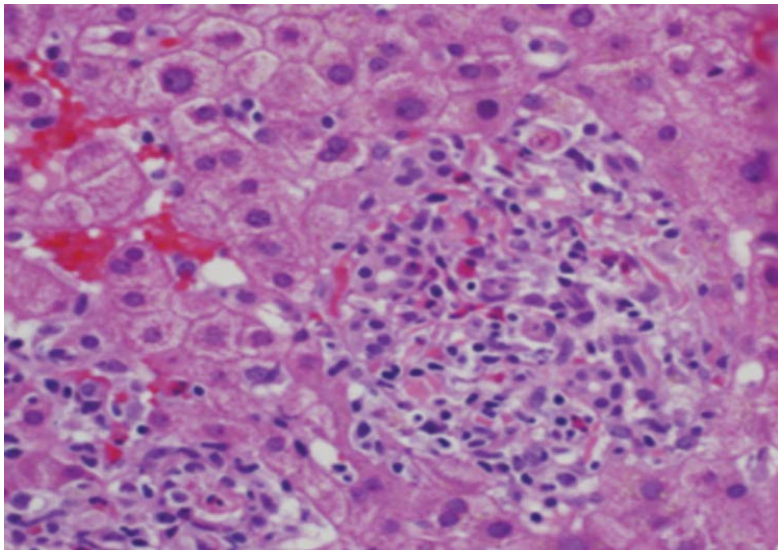


Liver Histology

- Marked zone 3 necrosis with numerous portal and lobular eosinophils
- Zone 3 cholestasis
- No fibrosis







Marumoto A, et al. Hawai'i Journal of Medicine & Public Health 2013;72(9)Supp4:30-33

Dose Relationship

Treatment	Dose	Treated Subjects	Subjects with DILI (%)
Placebo	-	6	0
Comparator*	400 mg	6	0
LY	25 mg	8	0
LY	75 mg	10	1 (10%)
LY	225 mg	9	5 (56%)

- Evaluation of the incidence of DILI in each dosing group demonstrated a clear dose-dependent trend of increasing likelihood of DILI with increasing dose
- Despite this trend, plasma concentrations of LY in DILI patients were comparable with those of patients who did not develop DILI within their dosing cohort

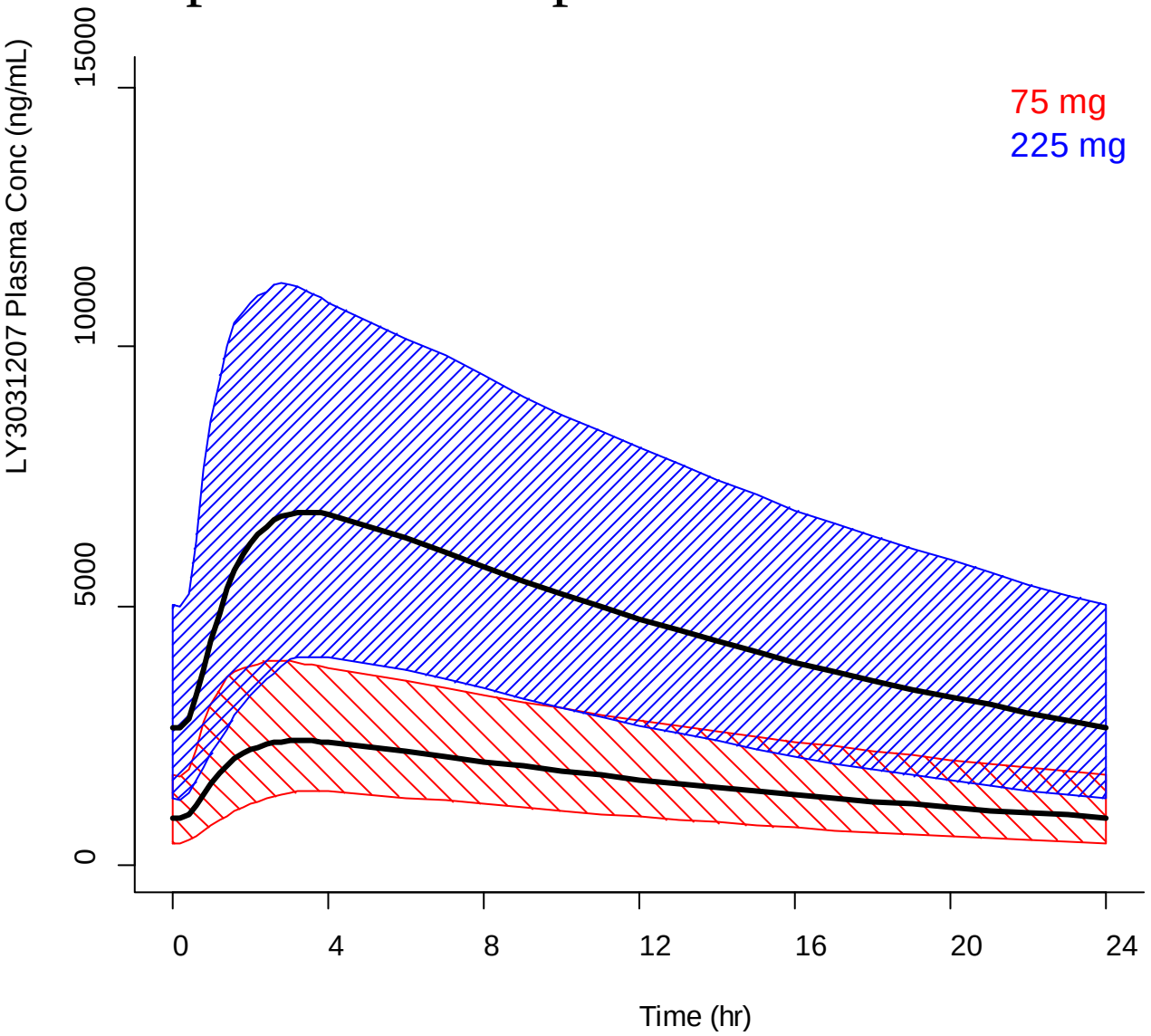
*Celecoxib 400mg once daily

Retrospective Analysis

- DILI patients were more likely to be older and female than patients who did not develop DILI

	DILI Cases (N=6)	Non-DILI Cases (N=13)	P-value
Age in years, mean (SD)	52.2 (10.15)	37.2 (11.79)	0.016
Female Sex, n, (%)	4 (66.7)	2 (15.4)	0.046
Race, n, (%)			0.442
White	2 (33.3)	7 (53.8)	
Asian	3 (50.0)	2 (15.4)	
Multiple	1 (16.7)	4 (30.8)	
Japanese Heritage, n, (%)			0.262
Yes	3 (50.0)	2 (15.4%	
No	3 (50.0)	11 (84.6)	
Baseline Weight in Kg, Mean (SD)	64.0 (15.65)	72.3 (11.43)	0.205

Simulated Steady State Concentration for Daily Oral Doses: No exposure overlap between 75 and 225 mg



Frequency of Eosinophilia by Treatment Group

Visit and Treatment	N	Subjects with Eos >6% n (%)
Baseline		
LY 25 mg	8	0 (0.0)
LY 75 mg	10	1 (10.0)
LY 225 mg	9	1 (11.1)
Placebo	6	0 (0.0)
Celecoxib	6	0 (0.0)
Post-treatment Assessment		
LY 25 mg	8	0 (0.0)
LY 75 mg	10	3 (30.0)
LY 225 mg	9	7 (77.8)
Placebo	6	0 (0.0)
Celecoxib	6	2 (33.3)

DILI Assessment

- Metabolism and Pharmacokinetics:
  - No unique human metabolites identified in blood samples of treated patients
  - Exposure was within the prediction range based on the single dose data
  - Subjects with DILI did not have greater exposure compared to subjects receiving the same dose who did not experience DILI
- Immunology profiling:

Endpoint	Patient Group	n	Mean [90% CI]	Comparison to DILI ratio [90% CI]	P value
IgE	DILI cases Non-DILI cases	6 12	1.54 [1.29, 1.84] 0.99 [0.87, 1.12]	0.64 [0.52, 0.80]	0.003
IgA	DILI cases Non-DILI cases	6 12	1.04 [0.92, 1.17] 1.02 [0.94, 1.11]	0.98 [0.85, 1.14]	0.837
IgG	DILI cases Non-DILI cases	6 12	1.02 [0.94, 1.11] 1.01 [0.96, 1.07]	0.99 [0.90, 1.10]	0.886
IgM	DILI cases Non-DILI cases	6 12	0.93 [0.81, 1.06] 1.06 [0.96, 1.16]	1.14 [0.97, 1.33]	0.177

Identification of LY Metabolites

- Profiling of human plasma using LC/MS* revealed the presence of LY and 3 metabolites (M1, M3, M5)
- In all plasma pools on all days, the parent drug was the predominant drug-related component
- M3 was generated from hydrolysis of an intermediate epoxide
- M3 was the most prominent metabolite observed and the only metabolite observed across all of the plasma pools
- Based on LC/MS ion intensity, the relative percentage of M3 was ≤2% of parent drug in the 25- and 75-mg groups and ranged from 2 to 10% in the 225-mg group

*LC/MS- Liquid Chromatography/ High Resolution Mass spectrometry

Comments

- Allergic/ hypersensitivity type DILI has been described with phenytoin, carbamazepine, lamotrigine, trimethoprim-sulphamethoxazole, etc.
- No consensus regarding nomenclature: DRESS syndrome (Drug Reaction with Eosinophilia and Systemic Symptoms); HSS (Hypersensitivity Syndrome); AHS (Anticonvulsant Hypersensitivity Syndrome); DIHS (Drug-Induced Hypersensitivity Syndrome)
- Immuno-allergic features are believed to be associated with worse outcome in DILI patients
- Immuno-allergic features (at least 2 of the 3*) were present in 11% of patients with hepatocellular DILI[1]

Immuno-allergic features:
Fever, Rash, Absolute eosinophilia >500/µL

1. Chalasani et al. Gastroenterology 2015

Summary

- A dose-response relationship has rarely been described with immune-mediated DILI
- This case series describes 6 patients who presented with acute hepatocellular hypersensitivity-type DILI which was strongly dose-dependent
- DILI occurred in about 56% of patients receiving the highest dose (225mg) , but in none of the patients receiving 25mg, and in only 1 (10%) receiving 75mg
- Exposure was significantly higher with higher doses, but was not different within the same dose-cohort
- DILI patients were more likely to be older and female than patients who did not develop DILI
- Although a specific metabolite may be involved with the DILI mechanism, additional work may be needed to clarify its role

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