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# Hy's Law and Pre-existing Liver Disease

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Mar 19, 2015



# Outline

- Brief overview
  - Hy's Law and Its Derivations
  - Hy's Law Track Record (FDA and Registry data)
- Chronic liver disease patient outcomes and the DILIN experience
- Hy's Law and chronic liver disease in the DILIN



# Hy's Law

- “Drug-induced hepatocellular jaundice is a serious entity. The mortality rate ranges from 10% to 50%.”
  - Hepatotoxicity, 2<sup>nd</sup> ed. Hy Zimmerman, 1999 (p. 432-3)

Pattern	AST or ALT	ALP
Hepatocellular	3-50 x ULN	1-3 x ULN
Cholestatic	1-3 x ULN	3-20 x ULN

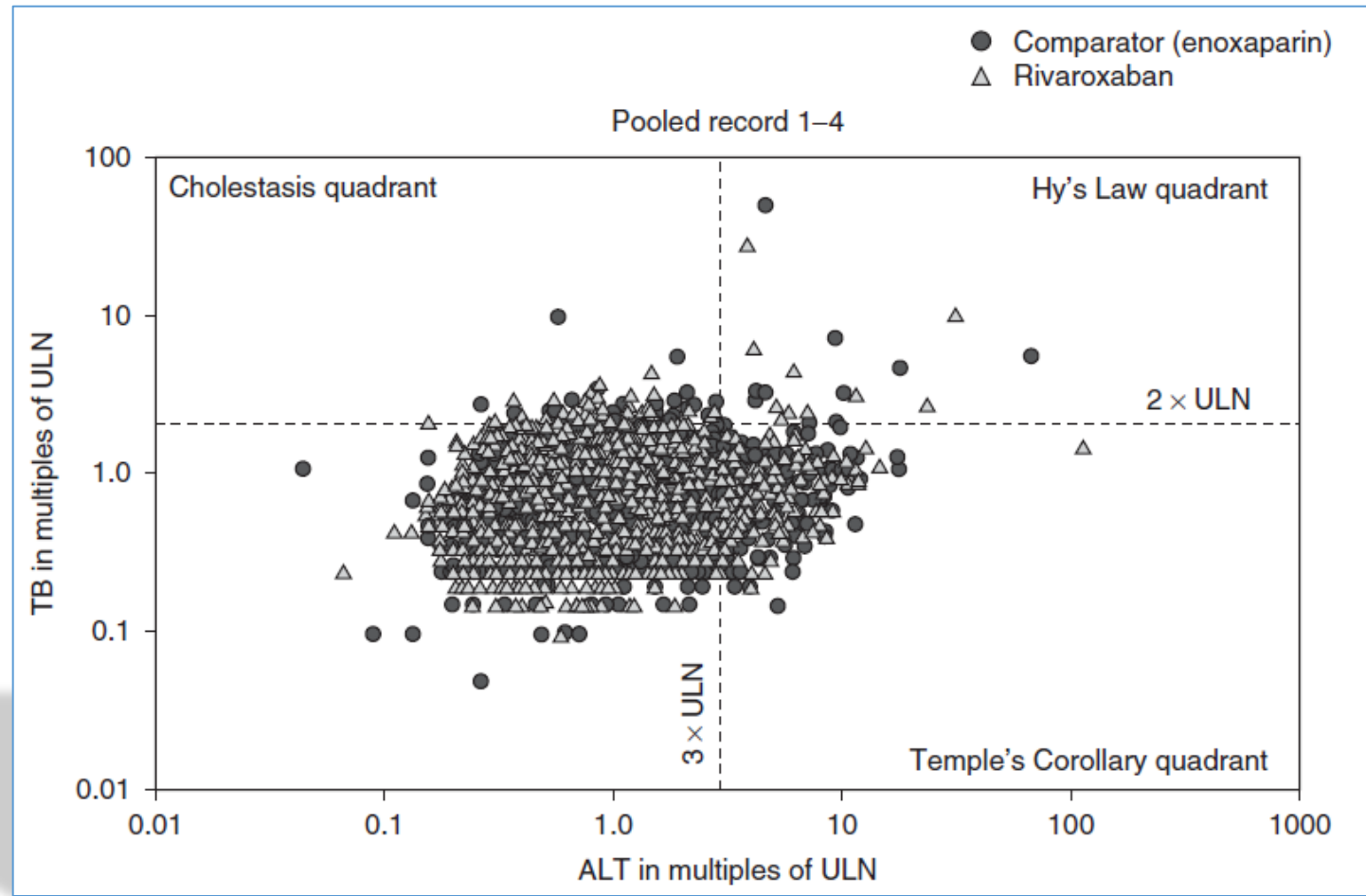


# Hy's Law according to the FDA

- ALT or AST > 3 x ULN
  - Bilirubin > 2 x ULN
  - No “initial findings of cholestasis (elevated serum ALP)”
  - No other reason for liver biochemistry elevations
- 
- DHHS, FDA (CDER & CBER), Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation – 2009.  
<http://www.fda.gov/downloads/Drugs/.../Guidances/UCM174090.pdf>



# eDISH Scattergram





# Hy's Law and Drug Trials

- ALT or AST  $> 3 \times$  ULN—good sensitivity; poor specificity
- Bilirubin  $> 2 \times$  ULN – improves specificity
- “2 case rule”
  - Two HL cases found in a trial is felt to be highly predictive of the agent causing acute liver failure.



# Hy's Law: Other Derivations

- US DILI Network (DILIN)\*
  - ALT > 3x ULN
  - Bilirubin > 2x ULN
  - ALP < 2x ULN
- Spanish DILI Registry^
  - ALT > 3x ULN
  - Bilirubin > 2x ULN
  - “excluding other (cholestatic) causes”
    - Or
  - {ALT or AST} x ULN/ ALP x ULN > 5
  - Bilirubin > 2x ULN

\* Fontana, RF et al. *Gastroenterology*, 2014 (The US DILIN)

^ Robles-Diaz, M, et al. *Gastroenterology*, 2014 (Spanish DILI Registry, SLatinDILI Networks, FETC)





# Track Record in Drug Trials:

Retrospective analyses & post-marketing

- Bromfenac
  - 2 HL cases in 1,195 in longer term use trial
  - Predicted a 1:5,000 to 1:10,000 rate of severe DILI
  - Post-marketing estimate: 1:10,000
- Troglitazone
  - 2 HL cases in 2,510 subjects in trial.
  - Risk estimated at 1:10,000
- Ximelagatran
  - ~2 HL cases in 1000 subjects seen in longer term use trials
  - Not approved in the US and later withdrawn in other countries

1. DHHS, FDA (CDER & CBER), Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation – 2009.

<http://www.fda.gov/downloads/Drugs/.../Guidances/UCM174090.pdf>

2. Lewis JH. Pharmacoepepi Drug Saf 2006



# Track Record in Registries

- US DILIN
  - 13.4% mortality for hepatocellular injury cases with *peak* bilirubin >2.5
- Spanish Registry
  - 8.3% ALF/mortality for HL cases (28 of 336)
  - 9.6% ALF/Mortality for “nR” criteria cases (27 of 282)
- Swedish Adverse Drug Reactions Advisory Committee
  - 9-10% mortality for “hepatocellular jaundice”.

Fontana, RJ, et al. *Gastroenterology* 2014  
Mercedes, RD, et al. *Gastroenterology* 2014  
Bjornsson, E, et al. *Hepatology* 2005



# DILI in Chronic Liver Disease

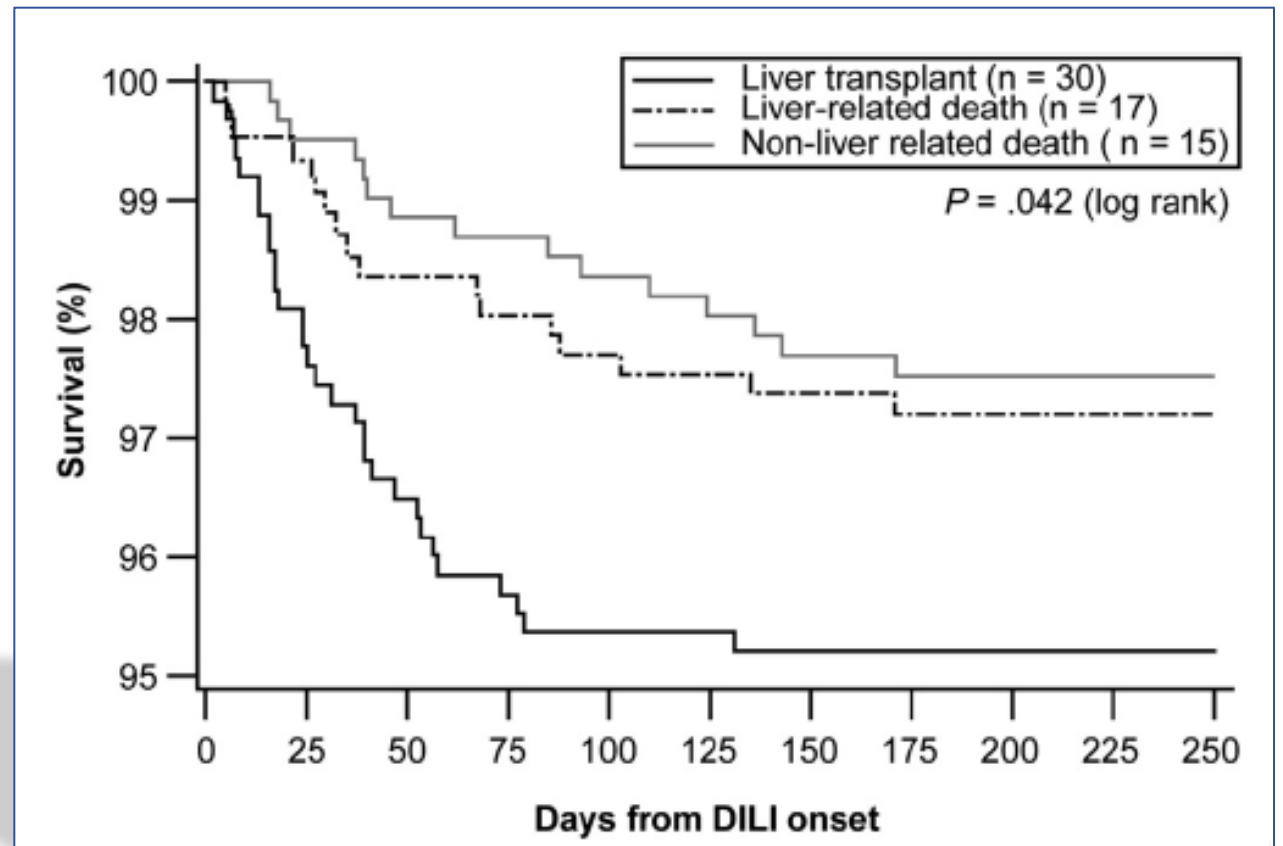
- Susceptibility and Course
  - “Stubborn misconception” that susceptibility is higher.
  - “...the addition of (DILI) to chronic liver disease would be troublesome.”
    - Hepatotoxicity, 2<sup>nd</sup> ed. Hy Zimmerman, 1999 (p. 430)
- Statin data suggests no increase in susceptibility.
- ?Increased susceptibility with anti-TB and HIV/ART therapy

# Idiosyncratic Drug-Induced Liver Injury Is Associated With Substantial Morbidity and Mortality Within 6 Months From Onset

Robert J. Fontana,<sup>1</sup> Paul H. Hayashi,<sup>2</sup> Jiezhun Gu,<sup>3</sup> K. Rajender Reddy,<sup>4</sup> Huiman Barnhart,<sup>3</sup> Paul B. Watkins,<sup>2</sup> Jose Serrano,<sup>5</sup> William M. Lee,<sup>6</sup> Naga Chalasani,<sup>7</sup> Andrew Stolz,<sup>8</sup> Timothy Davern,<sup>9</sup> and Jayant A. Talwakar,<sup>10</sup> on behalf of the DILIN Network

Gastroenterology 2014;147:96–108

- 660 DILI cases (definite, highly likely, or probable)
- At 6 month follow-up
  - 32 died (17 liver related)
  - 30 were transplanted





# Idiosyncratic Drug-Induced Liver Injury Is Associated With Substantial Morbidity and Mortality Within 6 Months From Onset

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*Gastroenterology* 2014;147:96–108

- Pre-existing liver disease more common in death/transplant outcome
  - 24% vs. 11% ( $p < 0.01$ )
  - 28% vs. 11% ( $p < 0.01$ ) when restricted to liver related death/transplant
- Hy's Law more common in death/transplant outcome.
  - 46% vs. 26% ( $p < 0.01$ )
  - 53% vs. 26% ( $p < 0.01$ ) when restricted to liver related death/transplant
- Multivariate analysis to predict liver related death/transplant
  - Hy's law fell out (ALT and bilirubin both in).
  - Pre-existing liver disease fell out (platelets and albumin in)



# Predicting Fatal Outcome

## Hy's Law in Chronic Liver Disease in the U.S. DILIN

- Cohort: n = 894 cases enrolled in DILIN
  - Only Definite, Highly likely and Probable cases.
- Subgroup analysis
  - Chronic liver disease (CLD) patients
    - HCV/HBV
    - NAFLD/Unexplained elevated liver biochemistries
  - Non-CLD patients
- Hy's Law
  - ALT > 3 x ULN
  - Bilirubin > 2 x ULN
  - ALP < 2 x ULN



# Predicting Fatal Outcome

## Hy's Law in Chronic Liver Disease in the U.S. DILIN

- Outcomes
  - DILIN Severity Index Score = 4 or 5
  - DILIN Severity Index Score = 5 (Death or Transplant)
- Death or Transplant
  - All cause, any time during follow-up.
  - Liver related death within 6 months or transplant within 6 months.



# DILIN Severity Index Score

Score	Description	Criteria
1	Mild	Patient has elevations in serum aminotransferase or alkaline phosphatase levels but total bilirubin is $< 2.5$ mg/dL and there is no coagulopathy (INR $< 1.5$ ).
2	Moderate	Patient has elevations in serum aminotransferase or alkaline phosphatase levels <u>and</u> total bilirubin is $\geq 2.5$ mg/dL <u>or</u> there is coagulopathy (INR $\geq 1.5$ ) without hyperbilirubinemia.
3	Moderate-Hospitalized	Patient has elevations in serum aminotransferase or alkaline phosphatase levels and total bilirubin is $\geq 2.5$ mg/dL or INR $\geq 1.5$ <u>and</u> the patient is hospitalized (or a pre-existing hospitalization is prolonged) because of the drug-induced liver injury.
4	Severe	<b>Patient has elevations in serum aminotransferase or alkaline phosphatase levels and total bilirubin is <math>\geq 2.5</math> mg/dL <u>and</u> there is at least one of the following:</b> <ul style="list-style-type: none"><li>• <b>signs of hepatic decompensation (INR <math>\geq 1.5</math>, ascites, or encephalopathy), <u>or</u></b></li><li>• <b>other organ failure believed to be associated with drug-induced liver injury event.</b></li></ul>
5	Fatal	<b>Patient dies or undergoes liver transplantation for drug-induced liver injury</b>



# Demographic and Clinical Characteristics

Fatal outcome: *Liver related death within 6 months and/or liver transplant within 6 months*

Characteristic	Non-fatal (n=855)	Fatal* (n=39)	Total (n=894)	p value
Age, years (mean, std. dev.)	48.3 (17.05)	55.6 (15.09)	48.6 (17.03)	<0.01
Gender (Female)	506/855 (59.2%)	20/39 (51.3%)	526/894 (58.8%)	0.33
Race: White or Caucasian	670/851 (78.7%)	29/39 (74.4%)	699/890 (78.5%)	0.61
Black or African American	98/851 (11.5%)	6/39 (15.4%)	104/890 (11.7%)	
Other	83/851 (9.8%)	4/39 (10.3%)	87/890 (9.8%)	
<b>Chronic Liver Disease</b>				
HCV	<b>34/855 (4.0%)</b>	<b>2/39 (5.1%)</b>	<b>36/894 (4.0%)</b>	<b>0.67</b>
HBV	<b>6/855 (0.7%)</b>	<b>1/39 (2.6%)</b>	<b>7/894 (0.8%)</b>	<b>0.27</b>
NAFLD	<b>16/855 (1.9%)</b>	<b>1/39 (2.6%)</b>	<b>17/894 (1.9%)</b>	<b>0.54</b>
Unexplained elevated LFTs	<b>29/855 (3.4%)</b>	<b>0/39</b>	<b>29/894 (3.2%)</b>	<b>0.63</b>
Other	<b>17/855 (2.0%)</b>	<b>5/39 (12.8%)</b>	<b>22/894 (2.5%)</b>	<b>NA</b>
Hy's Law	<b>231/791 (29.2%)</b>	<b>15/38 (39.5%)</b>	<b>246/829 (29.7%)</b>	<b>0.20</b>



# Demographic and Clinical Characteristics

Fatal outcome:

*All-cause deaths at anytime during follow-up &/or liver transplant at anytime during follow-up*

Characteristic	Non-fatal (n=832)	Fatal <sup>^</sup> (n=62)	Total (n=894)	p value
<b>Chronic Liver Disease</b>				
HCV	34/832 (4.1%)	2/62 (3.2%)	36/894 (4.0%)	1.00
HBV	6/832 (0.7%)	1/62 (1.6%)	7/894 (0.8%)	0.40
NAFLD	15/832 (1.8%)	2/62 (3.2%)	17/894 (1.9%)	0.33
Unexplained elevated LFTs	27/832 (3.2%)	2/62 (3.2%)	29/894 (3.2%)	1.00
Other	14/832 (1.7%)	8/62 (12.9%)	22/894 (2.5%)	NA
Hy's Law	219/771 (28.4%)	27/58 (46.6%)	246/829 (29.7%)	0.01



# Cohort: probable, highly likely, definite cases

- Outcome:
  - *All-cause mortality, anytime during follow-up or*
  - *Liver transplant, anytime during follow-up*
- Positive predictive value of Hy's Law: **11%**

	Fatal Outcome		Totals
	(+)	(-)	
HysLaw			
(+)	27	219	246
(-)	31	552	583
Totals	58	771	829

	%
Sensitivity	46.6
Specificity	71.6
<b>PPV</b>	<b>11.0</b>
NPV	94.7
Overall % w/ Fatal Outcome	7.0



# No Chronic Liver Disease Patients

- Outcome:
  - *All-cause mortality, anytime during follow-up or*
  - *Liver transplant, anytime during follow-up*
- Positive predictive value of Hy's Law: **9.5%**

HysLaw	Fatal Outcome		Totals
	(+)	(-)	
(+)	21	200	221
(-)	26	503	529
Totals	47	703	750

	%
Sensitivity	44.7
Specificity	71.6
<b>PPV</b>	<b>9.5</b>
NPV	95.1
Overall % w/ Fatal Outcome	6.3



# Chronic Liver Disease Patients

- Outcome:
  - *All-cause mortality, anytime during follow-up or*
  - *Liver transplant, anytime during follow-up*
- Positive predictive value of Hy's Law: **24.0%**

	Fatal Outcome		Totals
	(+)	(-)	
HysLaw			
(+)	6	19	25
(-)	5	49	54
Totals	11	68	79

	%
Sensitivity	54.5
Specificity	72.1
<b>PPV</b>	<b>24.0</b>
NPV	90.7
Overall % w/ Fatal Outcome	13.9



# Predicting Fatal Outcome Hy's Law and Chronic Liver Disease

- Outcome:
  - All-cause mortality, anytime during follow-up or
  - Liver transplant, anytime during follow-up

	Hy's Law PPV
Total Cohort	11.0%
No Chronic Liver Disease	9.5%
Chronic Liver Disease	24.0%



# Cohort: probable, highly likely, definite cases

- Outcome:
  - *Liver related death within 6 months and/or*
  - *Liver transplant within 6 months*
- Positive predictive value of Hy's Law: **6.1%**

	Fatal Outcome		Totals
	(+)	(-)	
HysLaw			
(+)	15	231	246
(-)	23	560	583
Totals	38	791	829

	%
Sensitivity	39.5
Specificity	70.8
<b>PPV</b>	<b>6.1</b>
NPV	96.1
Overall % w/ Fatal Outcome	4.6



# No Chronic Liver Disease Patients

- Outcome:
  - *Liver related death within 6 months and/or*
  - *Liver transplant within 6 months*
- Positive predictive value of Hy's Law: **5.0%**

HysLaw	Fatal Outcome		Totals
	(+)	(-)	
(+)	11	210	221
(-)	19	510	529
Totals	30	720	750

	%
Sensitivity	36.7
Specificity	70.8
<b>PPV</b>	<b>5.0</b>
NPV	96.4
Overall % w/ Fatal Outcome	4.0





# Chronic Liver Disease Patients

- Outcome:
  - *Liver related death within 6 months and/or*
  - *Liver transplant within 6 months*
- Positive predictive value of Hy's Law: **16.0%**

	Fatal Outcome		Totals
	(+)	(-)	
HysLaw			
(+)	4	21	25
(-)	4	50	54
Totals	8	71	79

	%
Sensitivity	50.0
Specificity	70.4
<b>PPV</b>	<b>16.0</b>
NPV	92.6
Overall % w/ Fatal Outcome	10.1



# Predicting Fatal Outcome Hy's Law and Chronic Liver Disease

- Outcome:
  - ***Liver related death within 6 months and/or***
  - ***Liver transplant within 6 months***

	Hy's Law PPV
Total Cohort	6.1%
No Chronic Liver Disease	5.0%
Chronic Liver Disease	16.0%



# Patients with Chronic HCV &/or HBV Infections

- Outcome:
  - *Liver related death within 6 months and/or*
  - *Liver transplant within 6 months*
- Positive predictive value of Hy's Law: **15.4%**

HysLaw	Fatal Outcome		Totals
	(+)	(-)	
(+)	2	11	14
(-)	1	22	23
Totals	3	33	36

	%
Sensitivity	66.7
Specificity	66.7
<b>PPV</b>	<b>15.4</b>
NPV	95.7
Overall % w/ Fatal Outcome	8.3



# Patients with NAFLD &/or Elevated Liver Enzymes

- Outcome:
  - *Liver related death within 6 months and/or*
  - *Liver transplant within 6 months*
- Positive predictive value of Hy's Law: **8.3%**

HysLaw	Fatal Outcome		Totals
	(+)	(-)	
(+)	1	11	12
(-)	0	28	28
Totals	1	39	40

	%
Sensitivity	100.0
Specificity	71.8
<b>PPV</b>	<b>8.3</b>
NPV	100.0
Overall % w/ Fatal Outcome	2.5



# Predicting Fatal Outcome Hy's Law and Chronic Liver Disease

- Outcome:
  - *Liver related death within 6 months and/or*
  - *Liver transplant within 6 months*

	Hy's Law PPV
Chronic Liver Disease	16.0%
HCV and/or HBV	15.4%
NAFLD/unexplained elevated liver enzymes	8.3%



# Summary

- Patients with a fatal outcome in the U.S. DILIN tended to have more baseline chronic liver disease and have more cases fitting Hy's Law.
- For those with chronic liver disease:
  - Hy's Law had a positive predictive value (PPV) of 24% for all-cause, anytime fatality or transplant.
  - Hy's Law had a positive predictive value (PPV) of 16% for liver related fatality or transplant within 6 months.
- Both of these PPVs were higher compared to those without chronic liver disease.
- The PPV for viral hepatitis patients may be higher than for NAFLD patients.



# Conclusions

- Hy's has a higher predictive value for fatality or transplant in patients with chronic liver disease than in those without.
- Whether and how this translates into overall incidence and risk for acute liver failure in a drug trial using chronic liver disease subjects is unclear, but suggests a continuing role for Hy's Law.
- Further research should focus on validation of these findings in other cohorts and adjusting Hy's Law parameters for best accuracy in those with chronic liver disease.