Chronic Liver Disease after Acute Hepatocellular DILI

Robert J. Fontana, MD
University of Michigan Medical Medical Center
DILI

• Natural history of acute DILI
  – Transplant/ death
  – Chronic DILI

• Chronic DILI
  – Incidence
    • Clinical features/ histology
    • Outcomes
  – Predictors

• Future treatments
DILI: A Clinical diagnosis
Requires a high index of suspicion

• **Inclusion**
  – Temporal association (most < 6 mon)
    • Dechallenge requires time
  – Drug latency, lab profile (R-value)
    • Polypharmacy common
  – Histology

• **Exclude more common causes**
  – HAV, HBV, HCV, pancreaticobiliary, ischemia, alcohol, AIH, NAFLD

• **No objective/confirmatory test**
DILI Management

• **Discontinue suspect medication** ¹
  - Supportive treatment (fluids, rest)
    • Urso given for cholestasis
    • Steroid given to sicker; more autoimmune/immunoallergic features ¹

• **Continued use of suspect drug ↑ risk of ALF and DILI progression on bx**
  - **39%** of biopsied pts (33) had ↑ ALT/ imaging at 5 yr ²

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¹ Am J Gastroenterol 2014
² Aithal Gut 1999; 44: 731
DILIN 2017

UO1 Cooperative Agreement NIDDK
J Hoofnagle, J Serrano, A Sherker
Inclusion criteria

• Age > 2
• Within 6 months of DILI onset *
• On 2 consecutive blood draws *
  – AST or ALT > 5 X ULN (baseline)
  – Alk phos > 2 X ULN (baseline)
  – T bilirubin > 2.5 mg/dl
• Chronic HBV, HCV, HIV allowed

* Exemption committee

(Fontana Drug Safety 2009; 32: 55)
DILIN Prospective Study

Case

DRUG A

0

DILI Onset

< 6

BL Visit

6

6 mon F/u

6 mon

12 & 24 mon F/u

As of 4/17 = 1800 1600 220 165

(Fontana Drug Safety 2009; 32: 55)
DILIN Prospective Study
9/04-5/13 (N=899 high causality cases)

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single prescription drug</td>
<td>62% *</td>
</tr>
<tr>
<td>Herbal &amp; dietary suppl (HDS)</td>
<td>16%</td>
</tr>
<tr>
<td>Multiple drugs</td>
<td>22%</td>
</tr>
</tbody>
</table>

*Antimicrobials 45%
- Amox-clavulanate 12%
- Isoniazid 6%
- Nitrofurantoin 5%

(Gastroenterology 2015; 148; 1340)
## DILIN Prospective Study

<table>
<thead>
<tr>
<th></th>
<th>N=899</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age *</td>
<td>49 + 17</td>
</tr>
<tr>
<td>% Female</td>
<td>59%</td>
</tr>
<tr>
<td>% Cau/ AA</td>
<td>79%/ 12%</td>
</tr>
<tr>
<td>Mean BMI (kg/m²)</td>
<td>27 + 6</td>
</tr>
<tr>
<td>% Hep /mixed/ chol</td>
<td>54/ 23/ 23</td>
</tr>
<tr>
<td>Peak ALT (U/ml)</td>
<td>1008 + 1221</td>
</tr>
<tr>
<td>Peak alk phos (U/ml)</td>
<td>406 + 388</td>
</tr>
<tr>
<td>Peak bilirubin (mg/dL)</td>
<td>13 + 12</td>
</tr>
<tr>
<td>% Liver biopsy</td>
<td>52%</td>
</tr>
</tbody>
</table>

* 6% < 18 years old

(Gastroenterology 2015; 148; 1340)
Natural History of DILI

Adults enrolled
9/04 to 8/11
N = 660
Causality 1, 2, 3

Liver Transplant/Death
within 6 months
N = 62 (9.4%)

Liver transplant*
N = 30 (48%)

Death
N = 32 (52%)

F/U > 6 months without
liver transplant/death
N = 598 (91.6%)

Chronic DILI
N = 113 (18.9%)

Non-chronic DILI
N = 485 (81.1%)

* 17/32 (53%) deaths liver related

(Gastroenterology 2014; 147: 96)
## Early death/ txp (9%)

<table>
<thead>
<tr>
<th></th>
<th>* Death/ liver txp N= 62</th>
<th>Alive 6 month n=598</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>53.0 + 15.6</td>
<td>50.4 + 15.9</td>
<td>0.28</td>
</tr>
<tr>
<td>% Caucasian</td>
<td>67.2%</td>
<td>81.6%</td>
<td>0.01</td>
</tr>
<tr>
<td>% Black</td>
<td>16.4%</td>
<td>10.6%</td>
<td></td>
</tr>
<tr>
<td>% Asian</td>
<td>9.8%</td>
<td>2.5%</td>
<td></td>
</tr>
<tr>
<td>% Diabetes</td>
<td>43.5%</td>
<td>23.4%</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>% Lung disease</td>
<td>29.0%</td>
<td>16.9%</td>
<td>0.02</td>
</tr>
<tr>
<td>% Malignancy</td>
<td>27.4%</td>
<td>8.5%</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>% Anti-mycobacter</td>
<td>9.4%</td>
<td>3.9%</td>
<td>0.044</td>
</tr>
<tr>
<td>Med AST</td>
<td>1093</td>
<td>287</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Med Bilirubin</td>
<td>9.5</td>
<td>4.9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>% Hepatocellular</td>
<td>71%</td>
<td>51%</td>
<td>0.17</td>
</tr>
<tr>
<td>% Steroids used</td>
<td>82%</td>
<td>37%</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

AUC= **0.89** (Asian ↓ albumin ↓ platelet ↑ AST ↑ bilirubin lung disease)

(Gastroenterology 2014; 147: 96)
Deaths in DILIN study
1089 high causality cases

• 107 fatalities within 2 years of DILI onset
  – 64% DILI primary role
  – 14% DILI contributory role
  – 22% unrelated to DILI

• Liver profile at death/ txp
  – 74% acute
  – 7% AoCLF

(Hayashi Hepatology 2017 in press)
# 68 Primary DILI Death cases

<table>
<thead>
<tr>
<th></th>
<th>ALF N=50</th>
<th>AoCLF N=5</th>
<th>Chronic liver failure N=9</th>
<th>Rapid cholestasis N=4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (yr)</td>
<td>48.7</td>
<td>60.1</td>
<td>51.5</td>
<td>62.3</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.2</td>
<td>27.3</td>
<td>28.6</td>
<td>33.0</td>
</tr>
<tr>
<td>% Hepatocellular</td>
<td>84%</td>
<td>60%</td>
<td>22%</td>
<td>50%</td>
</tr>
<tr>
<td>T Bilirubin onset</td>
<td>12.5</td>
<td>11.3</td>
<td>7</td>
<td>2.9</td>
</tr>
<tr>
<td>Time to death/ LT (d)</td>
<td>35</td>
<td>59</td>
<td>236</td>
<td>132</td>
</tr>
</tbody>
</table>

(Hayashi Hepatology 2017 in press)
## Chronic DILI (19%)

71% lab 17% imaging 26% clinical

<table>
<thead>
<tr>
<th></th>
<th>Chronic DILI N=113</th>
<th>Non-chronic N=485</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>49.7 ± 15.1</td>
<td>50.6 ± 16.1</td>
<td>0.58</td>
</tr>
<tr>
<td>% Caucasian</td>
<td>73.5%</td>
<td>82.9%</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>% Black</td>
<td>18.6%</td>
<td>8.7%</td>
<td></td>
</tr>
<tr>
<td>% Asian</td>
<td>3.5%</td>
<td>6.4%</td>
<td></td>
</tr>
<tr>
<td>% Anti-neoplastic</td>
<td>11.5%</td>
<td>3.1%</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Med Drug use (d)</td>
<td>51 (1,2343)</td>
<td>30 (1, 6971)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Alk phos (IU/L)</td>
<td>302 (41, 1730)</td>
<td>208 (35, 1952)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>% Cholestatic</td>
<td>42.5%</td>
<td>21.9%</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Peak bili (mg/dl)</td>
<td>13.7</td>
<td>7.9</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>% Steroids</td>
<td>45.5%</td>
<td>34.4%</td>
<td>0.04</td>
</tr>
</tbody>
</table>

**AUC = 0.75** (black, ↑ med use, ↑ alk phos, ↑ bilirubin, malignancy)

(Gastroenterology 2014; 147: 96)
Chronic DILI
N = 113 (21%)

Self-limited Acute DILI
N = 485

Followed > 6 months from DILI onset without LT/death
N = 598

Missing labs at 12 months from onset
N=14

Month 12

Persister
N=74

Resolver
N=25

Month 24

(Labs at 12 Month FU N=99)

Excluded
1) Ineligible (n=143)
2) Liver txp/ death (n=62)

DILIN Causality score (1,2,3) N=801

Month 6

Chronic DILI
N = 113 (21%)

Month 12

Study visit
Baseline

(Fontana AJG 2015: 110: 1450)
# Persistent liver injury

<table>
<thead>
<tr>
<th></th>
<th>Mon 12 Persisters N=74</th>
<th>Mon 12 Resolvers N=25</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>52.6</td>
<td>43.8</td>
<td>0.01</td>
</tr>
<tr>
<td>Duration drug use (d)</td>
<td>54</td>
<td>32</td>
<td>0.70</td>
</tr>
<tr>
<td>ALT at onset</td>
<td>275</td>
<td>553</td>
<td>0.01</td>
</tr>
<tr>
<td>Alk phos at onset</td>
<td>394</td>
<td>219</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>R-value onset</td>
<td>1.8</td>
<td>8.0</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Peak alk phos</td>
<td>599</td>
<td>246</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>% Steroids used</td>
<td>47%</td>
<td>44%</td>
<td>1.00</td>
</tr>
<tr>
<td>% Urso used</td>
<td>26%</td>
<td>12%</td>
<td>0.18</td>
</tr>
</tbody>
</table>

AUROC = 0.7 (Age, alk phos)

(Fontana AJG 2015: 110: 1450)
Serial Alk phos levels

(Fontana AJG 2015: 110: 1450)
Quality of Life Scores

(Fontana AJG 2015: 110: 1450)
Liver histology in Chronic DILI

- 12 with paired liver biopsies
  - Med time to 1st = 22 d  2nd =446 days
  - Age =48  70% female
  - 33% Diabetes  BMI =25.6 kg/m²

- 8 of 12 Ishak fib progression (397 days)
  - 7 bile duct loss

(Fontana AJG 2015: 110: 1450)
## Serial liver biopsies

<table>
<thead>
<tr>
<th>R value</th>
<th>1st biopsy</th>
<th>Time</th>
<th>2nd biopsy</th>
<th>IF progress</th>
</tr>
</thead>
<tbody>
<tr>
<td>45M azithromycin</td>
<td>62.6 Chronic hep</td>
<td>392</td>
<td>Chronic hep</td>
<td>0</td>
</tr>
<tr>
<td>37F tamoxifen</td>
<td>17 Steatohepat</td>
<td>246</td>
<td>Steatohepat</td>
<td>-3</td>
</tr>
<tr>
<td>38F celecoxib</td>
<td>8.4 Cholest hep</td>
<td>382</td>
<td>Chronic chol</td>
<td>0</td>
</tr>
<tr>
<td>20F azithromycin</td>
<td>7.3 Acute hep</td>
<td>283</td>
<td>Chronic chol</td>
<td>+2</td>
</tr>
<tr>
<td>64M amox-clav</td>
<td>6.8 Cholest hep</td>
<td>183</td>
<td>Chronic chol</td>
<td>+2</td>
</tr>
<tr>
<td>54F omeprazole</td>
<td>2.5 Cholest hep</td>
<td>331</td>
<td>Chronic chol</td>
<td>+2</td>
</tr>
<tr>
<td>70F lansoprazole</td>
<td>2.4 Cholest hep</td>
<td>217</td>
<td>Ductopenia</td>
<td>+1</td>
</tr>
<tr>
<td>53F bactrim</td>
<td>1.9 Chronic chol</td>
<td>490</td>
<td>Chronic chol</td>
<td>0</td>
</tr>
<tr>
<td>52M metaclopramide</td>
<td>1.8 Cholest hep</td>
<td>404</td>
<td>Chronic chol</td>
<td>+4</td>
</tr>
<tr>
<td>20F olanazapine</td>
<td>1.6 Cholest hep</td>
<td>633</td>
<td>Chronic chol</td>
<td>+4</td>
</tr>
<tr>
<td>56M glucoease</td>
<td>1.1 Chronic hep</td>
<td>522</td>
<td>Chronic chol</td>
<td>+2</td>
</tr>
<tr>
<td>58F ultravist vitamin</td>
<td>0.42 Steatohepat</td>
<td>246</td>
<td>Steatohepat</td>
<td>+2</td>
</tr>
</tbody>
</table>

( Fontana AJG 2015: 110: 1450)
## Chronic DILI worldwide

<table>
<thead>
<tr>
<th></th>
<th>DILIN (‘04- ’11)</th>
<th>Spanish (‘95- ’05)</th>
<th>Sweeden (‘70- ’04)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>660 high causality cases</td>
<td>493 RUCAM &gt; possible</td>
<td>712 initial survivors</td>
</tr>
<tr>
<td>Study design</td>
<td>Prospective</td>
<td>Prospective</td>
<td>Retro (chart review)</td>
</tr>
<tr>
<td>% Chronic DILI</td>
<td>19%</td>
<td>5.7%</td>
<td>3.4%</td>
</tr>
<tr>
<td>Definition</td>
<td>AST, ALT, Alk P &gt; ULN or biopsy at 6 mon</td>
<td>HC: &gt; 3 mon Chol: &gt; 6 mon LFTs</td>
<td>Clinical</td>
</tr>
<tr>
<td>Mean follow-up</td>
<td>6 -24 mon</td>
<td>20 mon</td>
<td>10 yrs</td>
</tr>
</tbody>
</table>

(1 Fontana Gastroenterology 2014; 147: 96)  
(2 Andrade Hepatology 2006: 44: 1581)  
(3 Bjornsson J Hepatology 2009; 50)
Chronic Liver Disease after Acute HC DILI

• DILI is uncommon with most drugs
  – 10% mortality within 6 months
  – With 50,000 DILI/yr in US, ~ 5,000 deaths/txp
    • Risk: ↑ AST, bili, INR

• Chronic DILI develops in 15-20%
  – Risk: ↑ AA and ↑ alk phos
    • Poorer QOL in mon 12 persisters vs resolvers
    • Progressive histology in some
  – Late deaths uncommon (2 yrs)

• Early therapeutic intervention worthy of study in high risk pts to reduce morbidity & mortality
Acknowledgments: NIDDK, DILIN investigators, and DCRI
DILIN Investigators

- UNC: P Watkins/ P Hayashi, H Bonkovsky
- Indiana University: N Chalasani/ R Vuppalanchi
- CPMC: T Davern/ M Bonacini
- University of Michigan: R Fontana/ H Conjeevaram
- UTSW - Dallas: W Lee/ D Rockey
- USC/ UCLA: A Stolz/ F Durazo
- Thomas Jefferson/ U Penn: V Navarro/ R Reddy
- Mayo Clinic: J Talwakar
- Mt Sinai: J Odin
- DCRI: H Barnhart/ H Tillman
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- NCI: D Kleiner

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Thank YOU !!!
Short-term Morbidity & Mortality

% Survival vs Days from DILI onset

- Liver transplant (n=30)
- Liver-related death (n=17)
- Non-liver related death (n=15)

p = 0.042 (log rank)
Improving Outcomes in Acute hepatocellular DILI

• Natural history of acute hepatocellular DILI is potentially severe
  – With 50,000 DILI in US/yr, an estimated 5,000 deaths/ liver txp within 6 mon \(^1\)

• Although mechanism/ pathogenesis of DILI remains largely unknown, interventional trial for high risk pts appears justified
  – ↑ALT, bili, INR at 2 to 4 wks after DILI onset
  – ? Antioxidant ? Anti-inflammatory

(1 Bjornsson Gastroenterol 2013; 144)
Alk phos levels in those with F/U biopsy

* Time of follow-up liver biopsy