The DILIN Prospective and Retrospective studies

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

• Retrospective study (ILIAD)
  – Recruitment & enrollment
  – Causality

• Prospective registry study
  – Recruitment & enrollment
  – Causality
  – 6 month follow-up
    • HCV & HEV testing
Challenges in studying DILI

• DILI is a rare disease
  – 10 – 15 per 100,000 pt-years \(^1\)
    • < 1% of acute liver injury \(^2\)
  – By drug, only 1 per \(10^4\) to \(10^6\) prescriptions

• Clinical diagnosis
  – Exclude competing causes
    • Dechallenge requires time
  – Variable latency, lab profile, & histology
    • Polypharmacy common
    • ? Quantity and quality of prior reports

• No objective/ confirmatory lab test

\(^1\) Sgro Hepatology 2002; 36: 451
\(^2\) Galan J Clin Gastro 2005; 39: 64
How to study a rare ADE

• Reports to regulatory agencies
  – Underreporting ? Data quality/confirmation ¹

• Retrospective approaches
  – Medical records search
    • ? Evaluation ? History ? Competing causes
  – Good specificity with flucloxacillin ²

• Population based studies

• Prospective multicenter registries ³,⁴
  – Interview, careful phenotyping
  – Expensive, labor intensive ? Referral bias

¹ Moore Arch Int Med 2007; 167
² Daly Nat Gen 2009; 41: 816
³ Andrade Gastroenterology 2005; 129: 512
⁴ Chalasani Gastroenterology 2008; 135
## DILI Registries Worldwide

<table>
<thead>
<tr>
<th>Country</th>
<th>Sweden</th>
<th>Spain</th>
<th>USA DILIN</th>
<th>Korea</th>
<th>Japan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years</td>
<td>‘75- ‘05</td>
<td>‘94 – ‘08</td>
<td>‘04-‘07</td>
<td>‘05-‘07</td>
<td>‘97-‘06</td>
</tr>
<tr>
<td>N</td>
<td>784</td>
<td>603</td>
<td>300</td>
<td>371</td>
<td>1,676</td>
</tr>
<tr>
<td>Structure</td>
<td>Govt registry</td>
<td>Prospect 45 ctrs</td>
<td>Prospect, 5 ctrs</td>
<td>Prospect 17 ctrs</td>
<td>Retro, many</td>
</tr>
<tr>
<td>% Hepato Mix/chol</td>
<td>52 21/29</td>
<td>55 21/25</td>
<td>56 20/ 24</td>
<td>59 20/21</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>58</td>
<td>54</td>
<td>48</td>
<td>49</td>
<td>55</td>
</tr>
<tr>
<td>% Died/ TXP</td>
<td>9.2%</td>
<td>5.4%</td>
<td>10.1 %</td>
<td>1.3 %</td>
<td>3.7%</td>
</tr>
<tr>
<td>Drugs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Antibiotic</td>
<td>27%</td>
<td>39%</td>
<td>45%</td>
<td>--</td>
<td>14%</td>
</tr>
<tr>
<td>% Hypolipid</td>
<td>1%</td>
<td>5%</td>
<td>3%</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>% Herbal</td>
<td>--</td>
<td>--</td>
<td>9%</td>
<td>73%</td>
<td>7%</td>
</tr>
</tbody>
</table>

(DILI Workshop Hepatology 2010; 52)
ILIAD: Idiosyncratic Liver Injury Associated with Drugs

• Enroll patients with significant liver injury due to drugs with established hepatotoxicity for mechanistic studies
  – Isoniazid, phenytoin, amoxicillin/clavulanate, valproic acid
  – TMP-SMZ, minocycline, nitrofurantoin, quinolones

• Inclusion criteria
  – Bilirubin >2.5 mg/dl
  – DILI onset after 1992
  – Brief study visit (blood sample)
ILIAD recruitment

- **89 patients enrolled (‘04-’11)**
  - 38% amox/clav 20% INH 9% valproate
- **Medical records search at sites**
  - Diagnostic/ billing codes +/- text search
  - ICD-9 codes low sensitivity & specificity
- **Outreach to sub-specialists**
  - Neurology, TB clinics/ networks
- **Limited direct referrals**
  - Some self-referrals (website)

(1 Am J Gastro 2004; 102: 1)
# DILIN Causality scores

<table>
<thead>
<tr>
<th></th>
<th>Retrospective Study (N=54)</th>
<th>Prospective Study (n= 597)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data quality score *</td>
<td>77 + 11</td>
<td>88 + 5</td>
</tr>
<tr>
<td>Definite (&gt; 95%)</td>
<td>33%</td>
<td>26%</td>
</tr>
<tr>
<td>Very likely (75-95%)</td>
<td>41%</td>
<td>42%</td>
</tr>
<tr>
<td>Probable (50-75%)</td>
<td>17%</td>
<td>17%</td>
</tr>
<tr>
<td>Possible (25-50%)</td>
<td>9%</td>
<td>11%</td>
</tr>
<tr>
<td>Unlikely (&lt; 25%)</td>
<td>0%</td>
<td>4%</td>
</tr>
</tbody>
</table>

* Range: 1 to 100

(DILIN database January 2011)
Prospective study - AIMS

• **#1** To identify bonafide cases of drug and herbal & dietary supplement (HDS) induced liver injury within 6 months of onset so that clinical data and samples can be collected for future mechanistic & genetic studies

• **#2** To identify clinical, immunological, and environmental risk factors for drug and HDS liver injury

(Fontana Drug Safety 2009; 32: 55)
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**

<table>
<thead>
<tr>
<th>0</th>
<th>DRUG A</th>
<th>&lt; 6</th>
<th>6</th>
<th>6 mon</th>
<th>12 &amp; 24 mon F/u</th>
</tr>
</thead>
<tbody>
<tr>
<td>DILI Onset</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BL Visit</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 mon F/u</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 &amp; 24 mon F/u</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
8 sites: 2 patients/site per month

N=882 January 2011
DILIN Prospective: Site enrollment

![Bar chart showing site enrollment and data entered for different institutions.](chart.png)
DILIN Recruitment Methods

• Local site PI
  – Conferences, e-mails, brochures
    • Outreach to MD’s, subspecialists, dinner meetings
  – Annual newsletters

• Network-wide
  – Journal ads, website
  – DILI symposia at meetings
  – Publications
  – Other research networks
  – FDA, CDC
## Implicated drugs

<table>
<thead>
<tr>
<th></th>
<th>‘04-’07 (n=300)</th>
<th>‘04-’11 (n=882)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single prescription drug</td>
<td>73% *</td>
<td>60%</td>
</tr>
<tr>
<td>Herbal &amp; dietary supp (HDS)</td>
<td>9%</td>
<td>14%</td>
</tr>
<tr>
<td>Multiple drugs</td>
<td>18%</td>
<td>26%</td>
</tr>
<tr>
<td>Implicated agents *</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antimicrobials</td>
<td>45%</td>
<td>44%</td>
</tr>
<tr>
<td>CNS drugs</td>
<td>15%</td>
<td>10%</td>
</tr>
</tbody>
</table>

* Augmentin, nitrofurantoin, isoniazid leading drugs

(Gastroenterology 2008: 135)
## DILIN Prospective Study

<table>
<thead>
<tr>
<th></th>
<th>’04-’07 (n=300)</th>
<th>’04- ’11 (n=882)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>48 + 18</td>
<td>48 + 18</td>
</tr>
<tr>
<td>% Female</td>
<td>60%</td>
<td>57%</td>
</tr>
<tr>
<td>% Cau/ AA</td>
<td>79%/ 11%</td>
<td>77%/ 12%</td>
</tr>
<tr>
<td>Mean BMI (kg/m²)</td>
<td>27 + 6</td>
<td>27 + 6</td>
</tr>
<tr>
<td>Median drug use (d)</td>
<td>42</td>
<td>30</td>
</tr>
<tr>
<td>% Hospitalized</td>
<td>60%</td>
<td>58%</td>
</tr>
<tr>
<td>% Liver biopsy</td>
<td>52%</td>
<td>51%</td>
</tr>
</tbody>
</table>

(Gastroenterology 2008: 135)
### DILIN Causality Scores

3 reviewers: Clinical narratives and diagnostic data

<table>
<thead>
<tr>
<th>Likelihood</th>
<th>‘04-’07 N=210</th>
<th>‘04-’11 N=597</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite (1)</td>
<td>&gt; 95%</td>
<td>32%</td>
</tr>
<tr>
<td>Highly likely (2)</td>
<td>75-95%</td>
<td>41%</td>
</tr>
<tr>
<td>Probable (3)</td>
<td>50-75%</td>
<td>13%</td>
</tr>
<tr>
<td>Possible (4)</td>
<td>25-50%</td>
<td>10%</td>
</tr>
<tr>
<td>Unlikely (5)</td>
<td>&lt; 25%</td>
<td>4%</td>
</tr>
</tbody>
</table>
Other causes of liver injury

• “Unlikely” DILI in 9 of 300 (3%) \(^1\)
  – 4 acute HCV

• HEV testing in 318 consecutive cases \(^2\)
  – 9 anti-HEV IgM + (2.8%)
    • 4 HEV RNA + (genotype 3)
    • 4 IgG + at 6 month
  – Mean age =67
    • 89% male, 22% HIV +

\(^1\) Gastroenterology 2008; 135: 1924
\(^2\) Davern et al submitted 2011
DILIN recruitment & enrollment: lessons learned

• **Retrospective study**
  – High data quality & valuable
  – Sustained enrollment challenging
    • Other networks? Physician/ public? ICD-10 DILI codes

• **Prospective DILIN study**
  – Consistent & steady enrollment
    • > 200 individual drugs
    • 26% multiple drugs
  – 6 month follow-up is valuable
    • Recommend HCV RNA testing
• 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
• DCRI                  H Barnhart/ H Tillman
• NIDDK                 J Hoofnagle/ J Serrano

• 2U01-DK065176-06 (Duke), 2U01-DK065201-06 (UNC), 2U01-DK065184-06 (Michigan), 2U01-DK065211-06 (Indiana), 5U01DK065193-04 (UConn), 5U01-DK065238-08 (UCSF/CPMC), 1U01-DK083023-01 (UTSW), 1U01-DK083027-01 (TJH/UPenn), 1U01-DK082992-01 (Mayo), 1U01-DK083020-01 (USC).
Thank YOU !!!