Epidemiology of Drug-induced Liver injury

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Drug-induced Liver injury

- Idiosyncratic DILI is a rare yet potentially severe cause of liver damage.
- Diagnosis is difficult and inaccurate in most instances.
- Any drug may be responsible.
- Predictive value of preclinical and clinical studies is limited.

References:
1. Sgro Hepatology 2002
2. Vuppallanchi AJG 2008
3. Meier EJCP 2005
The Phases of Drug Development

Most type A reactions detected here

Marketing Authorisation

Most type B reactions detected here

Number of subjects

PHASE 1  PHASE 2  PHASE 3  PHASE 4

50 volunteers  250 patients  2,000 patients  Many 1,000’s

50 volunteers  250 patients  2,000 patients  Many 1,000’s
The Rising incidence of DILI

Number of cases

- 1997-98: 37 cases
- 1998-00: 39 cases
- 2001-02: 47 cases
- 2003-04: 41 cases
- 2005-06: 67 cases
- 2007-08: 82 cases

Devarbhabi et al AJG 2010
DILI retrospective studies

- Usually have used the International Classification of Diseases (9th version) (ICD-9)
  - Very low specificity (1-5%), yielding highly variable estimates of DILI incidence
    - 41 cases per 100,000 persons per year of acute liver tests abnormalities attributed to drugs in the general population \(^1\)
    - 57/4209 (1.4%) of inpatients develop hepatotoxicity (ICD-10) \(^2\)
    - GPRD in UK 1,636,792 persons followed 5 years, 2.4 per 100,000 per year developed non fatal DILI \(^3\)

3. Hussaini EJCP 2007, 3 De Abajo BJCP 2004
Retrospective studies in DILI: limitations

- Underestimation of true frequency as DILI is often asymptomatic
- Selection bias: in referral centers patients with more severe DILI are detected
  - 77/1164 (6.6%) patients with liver disease seen in an outpatient clinic
  - 28/347 (8.1%) of jaundiced patients referred to the Jaundice Hotline in UK
  - 5/732 (0.7%) cases of jaundice admitted to hospital in a 2 year period

1. De Valle APT 2006
2. Hussaini EJCP 2007
3. Vuppallanchi AJG 2008
Prospective studies in DILI

FRANCE (3 y. study): 34 cases (82% outpatients) 2 deaths
Total Incidence = 139/10^6 per year (16 times > than the reported in France) Sgro et al Hepatology 2002

SPAIN (10 y. study prospective Registry):
Total Incidence = 34.2/10^6 per year
Serious reactions = 16.6/10^6 per year
Andrade et al Gastro 2005
Suspicion of DILI

Detailed History

Structured Report Form

- Underlying liver disease
- Drug addiction
- Alcohol consumption
- Blood transfusion
- History drug/herbal use

Expert's Ascertainment

Drug-related

Non Drug-related

Temporal relationship

Exclusion of liver causes

Risk Factors

Outcome

CI OMS scale

CIOMS scale

CIOMS scale

CIOMS scale
TO FILE THE INFORMATION

ACCESS DATABASE

EVALUATION AND FOLLOWUP OF A SIGNAL

INCLUSION IN THE REGISTRY

FEEDBACK AND REPORTING TO THE SAPNI SH FV SYSTEM

COORDINATING CENTER
H. CLINICO, SCHOOL MEDICINE, MALAGA

POSTAL MAIL / EMAIL

CLINICAL UNITS

TO FILE THE INFORMATION

COORDINATING CENTER
H. CLINICO, SCHOOL MEDICINE, MALAGA
Prospective studies: Spanish DILI Registry

Submitted DILI cases to the Spanish DILI Registry over a 15-year period
Causative drugs

1. Amox-clav
2. Flutamide
3. Ibuprofen

Antimicrobials 32%
CNS 15%
MS (NAIDS..) 14%
Others 20%
GI 8%
CVD 10%

1. Amox-clav
2. Trimethoprim SMZX/
Nitrofurantoin/
Isoniazid

Antimicrobials 45%
CNS 15%
Others 28%
CVD 8%
Herbals 9%

1. Lucena et al. Hepatology 2009
### Association Between Daily Doses of Oral Prescription Medications and Hepatic Adverse Events

<table>
<thead>
<tr>
<th>Number of Compounds Reported To Have Caused</th>
<th>( \leq 10 \text{ mg} ) ((n = 54))</th>
<th>(11-49 \text{ mg} ) ((n = 83))</th>
<th>(\geq 50 \text{ mg} ) ((n = 93))</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT &gt; 3 X ULN (n, %)</td>
<td>10 (19)</td>
<td>22 (27)</td>
<td>29 (31)</td>
<td>0.10</td>
</tr>
<tr>
<td>Jaundice (n, %)</td>
<td>18 (33)</td>
<td>33 (40)</td>
<td>42 (45)</td>
<td>0.16</td>
</tr>
<tr>
<td>Liver Failure (n, %)</td>
<td>9 (17)</td>
<td>10 (12)</td>
<td>30 (32)</td>
<td>0.009</td>
</tr>
<tr>
<td>Death (n, %)</td>
<td>6 (11)</td>
<td>9 (11)</td>
<td>26 (28)</td>
<td>0.004</td>
</tr>
<tr>
<td>Transplant (n, %)</td>
<td>0 (0)</td>
<td>2 (2)</td>
<td>12 (13)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Prescriptions (median in 2005)</td>
<td>4,746,500</td>
<td>4,938,000</td>
<td>3,733,000</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Source: Thompson’s Micromedex Drugdex System

Lammert et al. Hepatology 2008
### Relationship Between Daily Dose and Different Hepatic Events: Results from the Logistic Regression Analysis

<table>
<thead>
<tr>
<th>Outcome and Covariate</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Liver failure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compound</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \leq 10 \text{ mg} )</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11 – 49 mg</td>
<td>0.69</td>
<td>0.26 – 1.81</td>
<td>0.446</td>
</tr>
<tr>
<td>( \geq 50 \text{ mg} )</td>
<td>2.38</td>
<td>1.03 – 5.50</td>
<td>0.042</td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compound</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \leq 10 \text{ mg} )</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11 – 49 mg</td>
<td>0.97</td>
<td>0.33 – 2.91</td>
<td>0.961</td>
</tr>
<tr>
<td>( \geq 50 \text{ mg} )</td>
<td>3.10</td>
<td>1.19 – 8.12</td>
<td>0.021</td>
</tr>
<tr>
<td><strong>Transplant</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compound</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(&lt; 50 \text{ mg} )</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \geq 50 \text{ mg} )</td>
<td>10.00</td>
<td>2.18 – 45.8</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Source: Thompson’s Micromedex Drugdex System

Lammert et al. Hepatology 2008
Types of Liver Injury and Outcome Stratified According to Daily Dose: The SADRAC Data (n= 598)

<table>
<thead>
<tr>
<th></th>
<th>≤ 10 mg/day</th>
<th>11-49 mg/day</th>
<th>≥ 50 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of DILI cases</strong></td>
<td>53 (9%) (10%)*</td>
<td>85 (14%) (13%)*</td>
<td>460 (77%) (77%)*</td>
</tr>
<tr>
<td>Pattern of injury</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatocellular</td>
<td>34 (64.2%)</td>
<td>43 (50.6%)</td>
<td>231 (50.2%)</td>
</tr>
<tr>
<td>Cholestatic</td>
<td>13 (24.5%)</td>
<td>22 (25.9%)</td>
<td>124 (26.9%)</td>
</tr>
<tr>
<td>Mixed</td>
<td>6 (11.3%)</td>
<td>20 (37.8%)</td>
<td>104 (22.6%)</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death/liver transplantation</td>
<td>1 (2%)</td>
<td>8 (9.4%)</td>
<td>61 (13.2%)*</td>
</tr>
<tr>
<td>Survived</td>
<td>52 (98%)</td>
<td>77 (90.6%)</td>
<td>399 (86.8%)</td>
</tr>
</tbody>
</table>

**Top 200 prescribed medicines in Sweden in 2005**

<table>
<thead>
<tr>
<th></th>
<th>≤ 10 mg/day</th>
<th>11-49 mg/day</th>
<th>≥ 50 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion belonging to each dose group</td>
<td>22.5%</td>
<td>27.5%</td>
<td>37.5%</td>
</tr>
<tr>
<td>Median # of prescriptions</td>
<td>249,197</td>
<td>360,149</td>
<td>215,760</td>
</tr>
</tbody>
</table>

*Spanish DILI Registry

Lammert et al. Hepatology 2008

*p=0.03
Type of liver damage

**Spanish Registry**
(n=603)

- Hepatocellular: 329 (55%)
- Cholestatic: 149 (25%)
- Mixed: 125 (21%)

**DILIN**
(n=300)

- Hepatocellular: 169 (57%)
- Cholestatic: 68 (23%)
- Mixed: 61 (20%)

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1 Lucena et al. Hepatology 2009
2 Chalasani et al. Gastroenterology 2008
DILI incidence adjusted to age and sex

Lucena et al. Hepatology 2009
Type of liver damage according to sex in patients younger or older than 60 years of age (n=603)

- Cholestatic
- Hepatocellular
- Mixed

Lucena et al. Hepatology 2009
## Gender distribution

<table>
<thead>
<tr>
<th>Study</th>
<th>DILIN(^1)</th>
<th>Spanish Registry(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean age</strong></td>
<td>n=300</td>
<td>n=603</td>
</tr>
<tr>
<td>(48 years)</td>
<td></td>
<td>(53 years)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>Male</td>
<td>Male</td>
</tr>
<tr>
<td></td>
<td>40%</td>
<td>51%</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>Female</td>
</tr>
<tr>
<td></td>
<td>60%</td>
<td>49%</td>
</tr>
<tr>
<td><strong>Hepatocellular</strong></td>
<td>35%</td>
<td>49%</td>
</tr>
<tr>
<td></td>
<td>65%</td>
<td>51%</td>
</tr>
<tr>
<td><strong>Cholestatic</strong></td>
<td>50%</td>
<td>55%</td>
</tr>
<tr>
<td></td>
<td>50%</td>
<td>45%</td>
</tr>
<tr>
<td><strong>Mixed</strong></td>
<td>43%</td>
<td>54%</td>
</tr>
<tr>
<td></td>
<td>57%</td>
<td>46%</td>
</tr>
</tbody>
</table>

\(^1\) Chalasani et al. Gastroenterology 2008  
\(^2\) Lucena et al. Hepatology 2009
Type of amox-clav liver injury across countries

- **Spanish study** (N=69)
  - Hepatocellular: 25
  - Cholestatic: 21
  - Mixed: 23

- **Belgian study** (N=35)
  - Hepatocellular: 4
  - Cholestatic: 23
  - Mixed: 8

- **English study** (N=22)
  - Hepatocellular: 8
  - Cholestatic: 8
  - Mixed: 1

- **USA study** (N=18)
  - Hepatocellular: 7
  - Cholestatic: 6

- **French study** (N=15)
  - Hepatocellular: 4
  - Cholestatic: 11
  - Mixed: 2

Amoxicillin-clavulanate DILI according to age

Hepatocellular: <55 years = 63.6%, ≥55 years = 22.2%
Cholestatic: <55 years = 22.7%, ≥55 years = 37.8%
Mixed: <55 years = 13.6%, ≥55 years = 40%

p<0.003

Lucena, et al Hepatology 2006
Cumulated survival curves of hepatocellular and cholestatic/mixed cases of drug-induced liver injury

Andrade et al, Gastroenterology 2005
Fatal cases according to the type of liver injury

- **Spanish Registry (2005)**: 7, 5, 2
- **Swedish Registry (2005)**: 12.7, 7.8, 2.4
- **DILIN (2008)**: 7.5, 14.3, 2.1

Legend:
- Brown: Hepatocellular
- Cyan: Cholestatic
- Yellow: Mixed
<table>
<thead>
<tr>
<th></th>
<th>Fulminant outcome (n=18)</th>
<th>Other Presentations (n=428)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean age (range), y</strong></td>
<td>53 (14-83)</td>
<td>53 (13-88)</td>
<td></td>
</tr>
<tr>
<td><strong>Women, n(%)</strong></td>
<td>16 (89%)</td>
<td>201 (47%)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td><strong>Clinical presentation</strong></td>
<td>100%</td>
<td>69%</td>
<td>&lt;.003</td>
</tr>
<tr>
<td><strong>Jaundice, (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hepatocellular damage</strong></td>
<td>15 (83%)</td>
<td>243 (57%)</td>
<td>&lt;.028</td>
</tr>
<tr>
<td><strong>Laboratory parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Br (mg/dL)</strong></td>
<td>16.3± 10.7</td>
<td>7.5±7.5</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td><strong>ALT(XULN)</strong></td>
<td>30.4± 21.6</td>
<td>19.9±23.9</td>
<td></td>
</tr>
<tr>
<td><strong>Liver transplantation</strong></td>
<td>6 (37%)</td>
<td>2 (0.5%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Drug &lt;3y on the market</strong></td>
<td>3 (17%)</td>
<td>56 (13%)</td>
<td></td>
</tr>
</tbody>
</table>
### Risk factors for development of acute liver failure

<table>
<thead>
<tr>
<th>Variables</th>
<th>Coefficient</th>
<th>OR (95% CI)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female Sex</td>
<td>3.220</td>
<td>25.04 (4.14-151)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Hepatocellular</td>
<td>2.064</td>
<td>7.87 (1.68-36.9)</td>
<td>&lt;.009</td>
</tr>
<tr>
<td>damage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Bilirubin</td>
<td>0.143</td>
<td>1.15 (1.09-1.22)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

Constant = -8.7

Abbreviations: CI, confidence interval; OR, odds ratio.

Andrade et al, Gastroenterology 2005
Drug-induced acute liver failure in USA (1998-2007)

Demographics (n=132)
- Overweight (BMI 28.7)
- Women (70.5%)
- Overrepresentation of minorities

Presentation
- Deep jaundice (mean bilirubin 20.8 mg/dL)
- Moderate ALT increases (median 580 U/L)
- Rash/eosinophilia (16%), autoantibodies (22%)

Type of damage
- HC (78%), Ch (12%), Mx (10%)

Causative drugs
- Antimicrobials (INH, sulfa-drugs, nitrofurantoin) 36%
- Alternative (illicit), antiepileptics, antimetabolites, statins 35%

Outcome predict
- SS (27%), LTs (42%), Non LT-Death (31%)
Tx for drug-induced ALF in US: NOSD

Other drugs:
- Propylthiouracil (19)
- Disulfiram (9)
- Halothane (8)
- Herbal (6)
- Amitriptyline (2)
- Nefazodone (2)
- Methotrexate (5)
- Troglitazone (4)
- Methyldopa (5)
- Mercaptopurine or azathioprine (3)
- Fialuridine (3)
- Single cases*

Non-steroidal anti-inflammatory drugs:
- Diclofenac (3)
- Bromfenac (2)
- Ibuprofen (2)
- Single cases:
  - Etodolac
  - Naproxen
  - Indomethacin

Statins:
- Atorvastatin (3)
- Cervastatin (2)
- Simvastatin (2)
- Single cases:
  - Pravastatin
  - Ezetimibe
  - Fluvastatin

Antituberculosis:
- Isoniazid (48)
- Isoniazid plus another anti-tuberculosis drug (2)

Anti-epileptics:
- Phenytoin (20)
- Valproate (20)
- Carbamazepine (3)
- Single case: Felbamate

Antibiotics:
- Nitrofurantoin (12)
- Ketoconazole (8)
- Amoxicillin and clavulanate (5)
- Trimethoprim-sulfamethoxazole (2)
- Minocycline (2)
- Single cases:
  - Terbinafine
  - Ciprofloxacin
  - Telithromycin
  - Levofloxacin
  - Itraconazole
  - Moxifloxacin
Conclusions

- DILI is increasingly been recognized in clinical practice yet its true incidence is not well known
- Antibacterials is the drug class more frequently involved in DILI
- The DILI phenotype is influenced by age and sex
- Young women are more prone to hepatocellular DILI and older men to the cholestatic expression
- In DILI the hepatocellular expression, high bilirubin levels and female sex carry a worst prognosis
Network-based biomedical research centre working on liver and digestive diseases CIBERehd

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