Drug Induced Liver Injury and Stevens Johnson Syndrome

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SJS Symposium
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March 3-4, 2015
Drug-Induced Liver Injury

• ~3-10% of acute liver injury in the US
• Single, major cause of acute liver failure
• Common cause for a medication to be abandoned during development
• Common cause for withdrawal or restriction of use of an approved medication
• Frequently accompanies Stevens Johnson syndrome

March 2015
Etiology of Acute Liver Failure in the US Adult Registry (n = 2,102)

ALF Study Group, Jan 2014

- APAP: 974 cases, 46%
- Drug: 227 cases, 11%
- Hep B: 147 cases
- Hep A: 37 cases
- Autoimm: 144 cases
- Ischemic: 117 cases
- Wilson's: 26 cases
- Budd-Chiari: 15 cases
- Pregnancy: 18 cases
- Other: 145 cases
- Indeter: 252 cases

Other: 12%
Drug-Induced Liver Injury

- Two major forms: direct & idiosyncratic
  - Direct: intrinsically hepatotoxic agent; injury is frequent (1-100%), dose-related, reproducible in animal models, “expected”
  - Idiosyncratic: not inherently hepatotoxic, rare (1:1,000-1:1,000,000), not dose related, not reproducible in animals, “unexpected”

March 2015
Idiosyncratic Hepatotoxicity

- Unexpected outcome, not dose-related, rare
  - Isoniazid (~1:500)
  - Amoxicillin/Clavulanic acid (~1:2,500)
  - Diclofenac (~1:30,000)

- Idiosyncrasy: immunologic or metabolic

- Phenotypes: acute hepatitis, Hepatocellular, Cholestatic or “Mixed”

- Etiology, generally unknown

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Idiosyncratic Drug-Induced Liver Injury: Immunoallergic hepatitis

- Acute liver injury with
  - Rash, fever, facial edema, lymphadenopathy,
  - Eosinophilia, atypical lymphocytosis
- Typically short latency, 1-30 days
- Rash and fever may precede hepatic manifestations
- Injury is usually hepatocellular initially, but may evolve into a cholestatic pattern
Idiosyncratic Drug-Induced Liver Injury: Immunoallergic hepatitis: many names

- Hepatitis with simple drug rash
- Immunoallergic hepatitis
- Drug-induced hypersensitivity syndrome
- Anticonvulsant hypersensitivity syndrome
- DRESS
- Stevens Johnson syndrome
- Toxic epidermal necrolysis (TEN)

March 2015
Drug-Induced Liver Injury & SJS

- Have a lot in common
- Severe adverse events
- Rare
- Idiosyncratic, unexpected
- Sometimes overlap
- Clinical and Research Challenge

March 2015
Drug-Induced Liver Injury Network

- Created in 2003, Cooperative Agreement [NIDDK]
- Consortium of 5-8 Clinical Centers
- Data Coordinating Center
- Sample Repository, Genetics Core
- Aim: Collect and fully characterize cases of clinically apparent, drug-induced liver injury (phenotype) to allow for mechanistic studies into its etiology and potential prevention or treatment.
Prospective Study Enrollment
Target: 2 patients/center/month

Prospective Study Figure 1: Monthly Cumulative Patient Enrollment

N = 1434
Causality in Drug Induced Liver Injury

- DILI is a diagnosis of exclusion
- Compatible history
- Negative tests for hepatitis A, B, C and E
- Absence of alcoholism, shock, autoimmunity
- Imaging studies of liver and biliary tree
- Known cause and compatible signature
- No specific tests to prove causality
# Drug-Induced Liver Injury Causality Assessment

<table>
<thead>
<tr>
<th>Score</th>
<th>Causality</th>
<th>Percent</th>
<th>Legal Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Definite</td>
<td>≥95%</td>
<td>Beyond a reasonable doubt</td>
</tr>
<tr>
<td>2</td>
<td>Very Likely</td>
<td>75-94%</td>
<td>Clear and convincing</td>
</tr>
<tr>
<td>3</td>
<td>Probable</td>
<td>50-74%</td>
<td>Preponderance of the evidence</td>
</tr>
<tr>
<td>4</td>
<td>Possible</td>
<td>25-49%</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Unlikely</td>
<td>&lt;25%</td>
<td></td>
</tr>
</tbody>
</table>

Each case is reviewed and scored by 3 DILIN hepatologists independently; discordances are resolved by email or telephone discussions.

*March 2015*
### DILIN: First 1,068 Cases

- **899** were adjudicated as definite, highly likely or probable (83%)
- Caused by ~250 different agents
- Prescription drugs: 84%
- Herbals and Dietary Supplements: 16%
- Top 10 most common: 36%
- Top 25 most common: 50%

13% possible, 5% unlikely

*Chalasani et al Gastro 2015, in press*
Prescription Drug-Induced Liver Injury
Twenty most common causes

<table>
<thead>
<tr>
<th>Rank</th>
<th>Agent</th>
<th>No</th>
<th>Rank</th>
<th>Agent</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Augmentin</td>
<td>91</td>
<td>11</td>
<td>Phenytoin</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>Isoniazid</td>
<td>48</td>
<td>12</td>
<td>Methyldopa</td>
<td>11</td>
</tr>
<tr>
<td>3</td>
<td>Nitrofurantoin</td>
<td>42</td>
<td>13</td>
<td>Azathioprine</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>TMP/SMZ</td>
<td>31</td>
<td>14</td>
<td>Hydralazine</td>
<td>9</td>
</tr>
<tr>
<td>5</td>
<td>Minocycline</td>
<td>28</td>
<td>15</td>
<td>Lamotrigine</td>
<td>9</td>
</tr>
<tr>
<td>6</td>
<td>Cefazolin</td>
<td>20</td>
<td>16</td>
<td>Mercaptopurine</td>
<td>9</td>
</tr>
<tr>
<td>7</td>
<td>Azithromycin</td>
<td>18</td>
<td>17</td>
<td>Atorvastatin</td>
<td>8</td>
</tr>
<tr>
<td>8</td>
<td>Ciprofloxacin</td>
<td>16</td>
<td>18</td>
<td>Moxifloxacin</td>
<td>8</td>
</tr>
<tr>
<td>9</td>
<td>Diclofenac</td>
<td>15</td>
<td>19</td>
<td>Allopurinol</td>
<td>7</td>
</tr>
<tr>
<td>10</td>
<td>Levofloxacin</td>
<td>13</td>
<td>20</td>
<td>Amoxicillin</td>
<td>7</td>
</tr>
</tbody>
</table>

*Chalasani et al: in press 2015*
### Drug-Induced Liver Injury

**9 Cases of Stevens Johnson Syndrome**

<table>
<thead>
<tr>
<th>No</th>
<th>Agent</th>
<th>SJS</th>
<th>Jaundice</th>
<th>Fatal</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lamotrigine</td>
<td>EM vs SJS</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>Lamotrigine</td>
<td>DRESS vs SJS</td>
<td>Yes</td>
<td>Yes*</td>
</tr>
<tr>
<td>3</td>
<td>Lamotrigine</td>
<td>SJS</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>Azithromycin</td>
<td>SJS</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>Azithromycin</td>
<td>TEN</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>Carbamazepine</td>
<td>SJS/TEN</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>Moxifloxacin</td>
<td>SJS</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>Diclofenac</td>
<td>SJS/TEN</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>9</td>
<td>Nitrofurantoin</td>
<td>SJS</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>All</td>
<td></td>
<td></td>
<td>89%</td>
<td>44%</td>
</tr>
</tbody>
</table>

*Death from hepatic failure*
## Drug-Induced Liver Injury and SJS

<table>
<thead>
<tr>
<th>Feature</th>
<th>SJS Cases (9)</th>
<th>All DILI Cases (899)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>32 years</td>
<td>49 years</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>78%</td>
<td>59%</td>
</tr>
<tr>
<td>Race: White</td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>44%</td>
<td>79%</td>
</tr>
<tr>
<td>Asian American</td>
<td>33%</td>
<td>12%</td>
</tr>
<tr>
<td>Race: African American</td>
<td>33%</td>
<td>12%</td>
</tr>
<tr>
<td>Race: Asian American</td>
<td>22%</td>
<td>7%</td>
</tr>
<tr>
<td>Median time to onset</td>
<td>14 days (1-58)</td>
<td>36 days (1 day-10 yrs)</td>
</tr>
<tr>
<td>Jaundice</td>
<td>89%</td>
<td>70%</td>
</tr>
<tr>
<td>Fatal</td>
<td>44%</td>
<td>11%*</td>
</tr>
</tbody>
</table>

*Liver Transplantation in 4%*
### Drug-Induced Liver Injury & SJS

<table>
<thead>
<tr>
<th>Feature</th>
<th>Chalasani et al Indianapolis, US 2004-2012 (n=899)</th>
<th>Devarbhavi et al India, Banglore 1997-2013 (n=670)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SJS/TEN</td>
<td>9 (1%)</td>
<td>32 (5%)</td>
</tr>
<tr>
<td>Mean age</td>
<td>32 years</td>
<td>31 years</td>
</tr>
<tr>
<td>Female sex</td>
<td>78%</td>
<td>56%</td>
</tr>
<tr>
<td>Jaundice</td>
<td>89%</td>
<td>62%</td>
</tr>
<tr>
<td>Latency</td>
<td>3-58 days</td>
<td>&lt; 60 days</td>
</tr>
<tr>
<td>Drugs</td>
<td>Lamotrigine (3)</td>
<td>Phenytoin (8)</td>
</tr>
<tr>
<td></td>
<td>Azithromycin (2)</td>
<td>Dapsone (4)</td>
</tr>
<tr>
<td></td>
<td>Carbamazepine (1)</td>
<td>Carbamazepine (4)</td>
</tr>
<tr>
<td></td>
<td>Moxifloxacin (1)</td>
<td>SMZ/TMP (3)</td>
</tr>
<tr>
<td></td>
<td>Diclofenac (1)</td>
<td>Nevirapine (3)</td>
</tr>
<tr>
<td></td>
<td>Nitrofurantoin (1)</td>
<td>Allopurinol (2)</td>
</tr>
</tbody>
</table>

- **SJS/TEN**: Severe cutaneous adverse reactions, TEN - Toxic epidermal necrolysis
- **Mean age**: Average age of patients
- **Female sex**: Percentage of female patients
- **Jaundice**: Percentage of patients with jaundice
- **Latency**: Duration from drug exposure to onset of symptoms
- **Drugs**: Commonly linked drugs to SJS/TEN
Lamotrigine

- Accounted for 12 of the 899 cases of DILI
- 11 had DRESS (7), SJS (3) or drug rash (1)
- Median age, 26 years; 75% women
- 63% white, 25% Afr Am, 13% Asian
- Median latency 23 days (8-117 days)
- Jaundice 83%
- Fatality 8%
Spectrum of Drug Induced Liver Injury

- **Acute Liver Failure**
- **Liver Injury with Jaundice**
- **Symptomatic Liver injury without Jaundice**
- **Asymptomatic rise in Serum Enzymes**

*Severe clinically apparent cases represent the “tip of the iceberg”*
Perhaps SJS & TEN represent the “tip of the iceberg”
Drug-Included Liver Injury & SJS

- The 9 patients with SJS were often exposed to multiple other medications some of which have been implicated in SJS
- Number of other agents, 0-14, mean = 5
- Anticonvulsants: clonazepam, levetiracetamin, phenytoin, pregabalin, valproate
- Analgesics: acetaminophen, ibuprofen, meloxicam
- Antibiotics: cephalosporins, clindamycin, doxycycline, erythromycin, fluoroquinolones, penicillin, piperacillin
- Psychotrophic: alprazolam, amitryptyline, aripiprazole, escitalopram, fluoxetine, lithium, lorazepam, methylphenidate, quetiapine, trazodone, ziprasidone

March 2015
LiverTox
Clinical and Research Information on Drug-Induced Liver Injury
www.livertox.nih.gov
LiverTox provides up-to-date, accurate, and easily accessed information on the diagnosis, cause, frequency, patterns, and management of liver injury attributable to prescription and nonprescription medications and herbal products. The LiverTox website provides a comprehensive resource for physicians and their patients, and for clinical academicians and researchers who specialize in idiosyncratic drug-induced hepatotoxicity. For complete information, see About.
LiverTox

Drug Sections (~750 currently)

- Overview of the drug (1-2 pages)
  - Background
  - Hepatotoxicity
  - Mechanism of Injury
  - Outcome and Management
- Representative cases
- Liver Histology
- Chemical structure
- Link to Product label (package insert)
- Annotated references with links
DRUG RECORD

DICLOFENAC

- Overview
- Case Reports
- Case Reports Submitted to LiverTox
- Product Information
- Chemical Formula and Structure
- References
- Other Reference Links

OVERVIEW

Diclofenac

Introduction

Diclofenac is a commonly used nonsteroidal antiinflammatory drug (NSAID) used for the therapy of chronic forms of arthritis and mild-to-moderate acute pain. Therapy with diclofenac in full doses is frequently associated with mild serum aminotransferase elevations and, in rare instances, can lead to serious clinically apparent, acute or chronic liver disease.
Case 1. Elevations in serum aminotransferase levels during first month of diclofenac therapy. [Modified from a case in the database of the Drug-Induced Liver Injury Network]

A woman in her 30s with ankylosing spondylitis was started on diclofenac in a dose of 75 mg twice daily. One week later, although asymptomatic, she was found to have raised serum aminotransferase levels and the drug was discontinued. Viral and autoimmune hepatitis serologies were negative. Ultrasound was normal. During the following month, her ALT levels returned to baseline. She had previously tolerated ibuprofen and nabumetone without difficulty.

**Key Points**

**Medication:** Diclofenac 75 mg orally twice daily  
**Pattern:** Hepatocellular (R=9)  
**Severity:** 1+ (never jaundiced, never hospitalized)  
**Latency:** Several days  
**Recovery:** Complete recovery 1 month after stopping the medication  
**Other medications:** Ibuprofen

**Laboratory Values**

<table>
<thead>
<tr>
<th>Time After Starting</th>
<th>Time After Stopping</th>
<th>ALT (U/L)</th>
<th>Alk P (U/L)</th>
<th>Bilirubin (mg/dL)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre</td>
<td>0</td>
<td>49</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Diclofenac started</td>
</tr>
<tr>
<td>7 days</td>
<td>0</td>
<td>255</td>
<td>79</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>9 days</td>
<td></td>
<td>253</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 days</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td>Diclofenac stopped</td>
</tr>
<tr>
<td>16 days</td>
<td>6 days</td>
<td>275</td>
<td>84</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>4 weeks</td>
<td>17 days</td>
<td>71</td>
<td>89</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>6 weeks</td>
<td>1 month</td>
<td>37</td>
<td>73</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>Normal Values</td>
<td></td>
<td>&lt;42</td>
<td>&lt;115</td>
<td>&lt;1.2</td>
<td></td>
</tr>
</tbody>
</table>
Clinical cases of drug-induced liver injury that have been submitted to LiverTox ("Submit a Case Report") are available for review. Most of these reference cases are from the Drug-Induced Liver Injury Network, but others are from users of LiverTox who have submitted data from an actual clinical case. All cases have been reviewed and cleared of personal identifiers and a brief comment added by the LiverTox editors. Click on the following link to view the submitted case reports that have been made publically available.

Submitted Cases on Diclofenac

Top of page
REFERENCES

Diclofenac

References Last Updated: 16 April 2014

1. Zimmerman HJ. Drugs used to treat rheumatic and musculospastic disease. The NSAIDS. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 517-41. (Review of hepatotoxicity of NSAIDs published in 1999 mentions that more than 60 cases of diclofenac hepatotoxicity have been appeared in the literature and 180 were known to the FDA; clinical features resemble acute hepatitis with hepatocellular enzyme elevations; a disproportional number of cases occur in women with osteoarthritis).


LiverTox Status: 2015

- Official release: October 2012
- Current web activity: 115,000 unique visitors per month
- 750 agents described
- 1.3 million words
- 13,000 annotated references
- 1,000 clinical cases

March 2015
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