The Burden of Drug Induced Liver Injury

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I have no financial relationships to disclose within the past 12 months relevant to my presentation

AND

My presentation does not include discussion of off-label or investigational use
Drug Induced Liver Injury in France

*Sgro et.al. Hepatol 2002*

- 81,300 followed prospectively over 3 years
- 95 suspected DILI cases
  - Antibiotics 25%
  - Psychotropics 23%
  - Hypolipidemetics 13%
  - Non-steroidalals 10%

- Incidence Data
  - 14 to 24 per 100,000
  - 16 times the rate of passive surveillance
  - Translates to 40,000 cases per year in the US
Barriers to Accurate Estimates of the Burden of DILI

- Lack of recognition
- Underreporting
- Rare events
Abnormal liver tests are common, but who is at risk for severe disease? (FDA Guidance for Industry, 2009 – Drug discontinuation parameters)

- ALT or AST >8xULN
- ALT or AST >5xULN for more than 2 weeks
- ALT or AST >3xULN and (TBL >2xULN or INR >1.5)
- ALT or AST >3xULN with symptoms
Diagnostic Approach to DILI

1. Complete history
2. Agent must precede liver injury
3. Exclude other causes of liver disease
4. Stop the agent, the patient improves
5. Injury recurs upon reexposure
Post-Marketing Reporting for DILI

U.S. Food and Drug Administration

Spontaneous Reporting of Adverse Events via MEDWATCH

Center for Drug Evaluation and Research

Center for Food Safety and Applied Nutrition
Recent U.S. **Withdrawals** and **Warnings** due to Liver Injury

- Bromfenac
- Troglitazone
- Kava kava
- Pemoline
- Felbamate
- Zileuton
- Trovafloxacin
- Benoxaprofen

- Propylthiouracil
- Interferon beta-1a
- Telithromycin
- Duloxetine
Drug Induced Liver Injury in Iceland

*Bjornsson E, et al. Gastroenterology 2013*

- Two Year Prospective study
- Reporting by all Icelandic providers
- Competing etiologies excluded
- Prescription information centrally available
- ALT or AST > 3 ULN or AlkP > 2 ULN as the entry criteria
Drug Induced Liver Injury in Iceland

*Bjornsson E, et al. Gastroenterology 2013*

- Annual incidence 19.1 cases per 100,000 inhabitants
- Age related increase in the incidence of DILI
- No relationship with gender, alcohol use
- Amoxicillin/clavulanate most common
- Herbal & Dietary Supplements (HDS) second most common
What we’ve learned

• Diagnosis of DILI requires a stepwise approach.
• Reporting of injury is important.
• Incidence is approx. 19 per 100,000 people.
• Amoxicillin/clavulanate is the most common culprit; HDS are second most common.
• Limitations to knowledge:
  – Epidemiological studies were in homogeneous populations.
  – Cohorts had low rates of alcohol and other comorbidities.
  – “HDS” are poorly characterized.
  – Increasing incidence of DILI with age may be artificial.
Incidence of Drug Induced Liver Injury and Mean Prescription Rate by Age: Iceland 2010-11

from Björnsson et al: 2013
DILIN Study Procedures

• Prospective enrollment
• Entry criteria
  • Liver injury within 6 months
  • Liver Injury defined as:
    • ALT or AST > 5xULN, or Alk Phos > 2xULN
    or
    • Any elevated ALT, AST, or Alk Phos with total bilirubin (TB) > 2.5 mg/dL or INR > 1.5
• Baseline, 6, 12 month study visits
  – History, exam, lab work
• Causality assessment via structured expert opinion
DILIN Study Cohort
September 2004 to May 2013

1257 subjects

1091 subjects
Completed Causality Assessment

899
Confirmed cases

142

Chalasani et. al. ACG Presentation 2014
## Top 10 therapeutic classes and individual agents to cause DILI in the USA (N=899)

<table>
<thead>
<tr>
<th>Therapeutic Class</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Antimicrobials</td>
<td>408</td>
</tr>
<tr>
<td>2 Herbal and dietary suppl.</td>
<td>145</td>
</tr>
<tr>
<td>3 Cardovascular agent</td>
<td>88</td>
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<tr>
<td>4 Neurlogical agents</td>
<td>82</td>
</tr>
<tr>
<td>5 Anti-neoplastic</td>
<td>49</td>
</tr>
<tr>
<td>6 Analgesics</td>
<td>33</td>
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<tr>
<td>7 Immunomodulatory</td>
<td>27</td>
</tr>
<tr>
<td>8 Endocrine</td>
<td>20</td>
</tr>
<tr>
<td>9 Rheumatologic</td>
<td>13</td>
</tr>
<tr>
<td>10 Gastrointestinal</td>
<td>12</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Individual agent</th>
<th>n</th>
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</thead>
<tbody>
<tr>
<td>1 Amox-Clavulanate</td>
<td>91</td>
</tr>
<tr>
<td>2 Isoniazid</td>
<td>48</td>
</tr>
<tr>
<td>3 Nitrofurantoin</td>
<td>42</td>
</tr>
<tr>
<td>4 TMP/SMX (Bactrim)</td>
<td>31</td>
</tr>
<tr>
<td>5 Minocycline</td>
<td>28</td>
</tr>
<tr>
<td>6 Cefazolin</td>
<td>20</td>
</tr>
<tr>
<td>7 Azithromycin</td>
<td>18</td>
</tr>
<tr>
<td>8 Ciprofloxacin</td>
<td>16</td>
</tr>
<tr>
<td>9 Levofloxacin</td>
<td>13</td>
</tr>
<tr>
<td>10 Diclofenac</td>
<td>12</td>
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</tbody>
</table>
Temporal Trends in DILIN

![Bar chart showing temporal trends in herbal and dietary supplements vs conventional drugs from 2004-2005 to 2010-2012.](image-url)
DILIN Experience 2013
262 HDS Consumed by 136 Patients

- Bodybuilding: 30%
- Weight Loss: 19%
- Depression: 33%
- Sexual Performance: 2%
- GI Upset: 2%
- Immune Support: 4%
- Joint support: 3%
- Chinese Herbs: 4%
- Miscellaneous: 4%
Temporal Trends in DILIN

Trend for Bodybuilding HDS: p=0.01
Trend for Other HDS: p=0.05
Outcomes of HDS Associated Liver Injury

*\( p < .05 \), representing difference among groups
What we’ve learned from the DILIN

• Antibiotics are the most common cause of liver injury in the study cohort; HDS second.
• The incidence of HDS liver injury *may* be rising.
• Liver injury due to non-bodybuilding HDS is more severe than injury from conventional drugs.
• Limitations to the DILIN data:
  – Little is known about HDS composition and safety.
  – DILIN is not population-based; we cannot give estimates of disease burden.
  – DILIN is not a surveillance program.
Drug-Induced Immunoallergic Hepatitis During Combination Therapy With Daclatasvir and Asunaprevir

Yohei Fujii, Yoshihito Uchida, and Satoshi Mochida
Outbreak of Severe Hepatitis Linked to Weight-Loss Supplement OxyELITE Pro

Marina M. Roytman, MD\textsuperscript{1,2}, Peter Pörzgen, PhD\textsuperscript{1}, Christine L. Lee\textsuperscript{2}, Leslie Huddleston, PA-C\textsuperscript{1}, Timothy T. Kuo, MD\textsuperscript{1}, Peter Bryant-Greenwood, MD\textsuperscript{3}, Linda L. Wong, MD\textsuperscript{4} and Naoky Tsai, MD\textsuperscript{1,2}

AJG Aug 2014

- Dietary supplement for weight loss or muscle building
- MMWR: 29 cases, 1 death and 2 transplants
SCOPRI
HERBALIFE
PRENDITI CURA DEL TUO BENESSERE
HERBALIFE.IT
Herbal and Dietary Supplement Induced Liver Injury

The DILIN Agenda

• Which products and ingredients cause injury?

• How do they cause injury?
  – Idiosyncrasy
  – Dose-related
  – Adulteration or contamination
  – Genetic susceptibility

• How can injury be prevented?
  – Use a drug development paradigm
  – Educate public and providers
  – Change regulation

• What is the true burden of disease?
Liver Injury from Herbal and Dietary Supplements

NIH-AASLD Workshop

May 4 – 5, 2015
Lister Hill Auditorium
NIH Campus
Bethesda, MD

Organizers
Victor Navarro
Jay Hoofnagle
Jose Serrano

www.niddk.nih.gov/news/events-calendar/HDS
The Delaware Liver Injury Study
Prospective Surveillance for Drug and Dietary Supplement Induced Liver Injury in Delaware

• Aim:
  – To determine the yearly incidence of drug and dietary supplement induced liver injury in the U.S.

• Methods:
  – Active reporting of suspected cases through Delaware Gastroenterology practices
  – Case record review
  – On-site patient interview and phlebotomy
  – Six and 12 month follow up
The Burden of Drug Induced Liver Injury

Summary

• Better estimates of the incidence of drug and dietary supplement induced liver injury are needed; efforts are underway.

• Antibiotics remain the most common cause for liver injury; HDS are increasingly recognized as causes.

• Future research efforts must focus on liver injury from HDS.
Mille Grazie!
Thank you!