The Future Outlook to DILI Research — From The Perspective of China

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DILI in General Population

Table 1. The Crude Annual Incidence During the Study Period and the Age-Standardized Incidence During the 2-Year Study Period

<table>
<thead>
<tr>
<th>Incidence of DILI</th>
<th>Per 100,000</th>
<th>Number of individuals in each age group</th>
<th>95% CI</th>
<th>95% CI</th>
<th>Mean prescription rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 96</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>19.1</td>
<td>251,860</td>
<td>15.4</td>
<td>23.3</td>
<td></td>
</tr>
<tr>
<td>Age-standardized incidence by age groups</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>15–24 (n = 8)</td>
<td>8.5</td>
<td>46,831</td>
<td>3.7</td>
<td>16.8</td>
<td>0.9</td>
</tr>
<tr>
<td>25–39 (n = 17)</td>
<td>12.6</td>
<td>67,600</td>
<td>7.3</td>
<td>20.1</td>
<td>1.2</td>
</tr>
<tr>
<td>40–59 (n = 31)</td>
<td>18.8</td>
<td>82,546</td>
<td>12.8</td>
<td>26.7</td>
<td>2.4</td>
</tr>
<tr>
<td>60–69 (n = 18)</td>
<td>32.6</td>
<td>27,622</td>
<td>18.7</td>
<td>51.5</td>
<td>4.8</td>
</tr>
<tr>
<td>70–79 (n = 13)</td>
<td>39.9</td>
<td>16,282</td>
<td>21.3</td>
<td>68.3</td>
<td>7.3</td>
</tr>
<tr>
<td>80–106 (n = 9)</td>
<td>41.0</td>
<td>10,979</td>
<td>18.7</td>
<td>77.8</td>
<td>9.3</td>
</tr>
</tbody>
</table>

- Less than 20/100,000
- The incidence increased in the elder people
Drug Can Cause All Kinds of Liver Injury We Have Ever Known

- Immunoallergic hepatitis
- Autoimmune hepatitis-like
- Acute hepatic necrosis
- Acute viral hepatitis-like
- ALF
- Cholestatic hepatitis
- Bland cholestasis
- Acute fatty liver with lactic acidosis
- Nonalcoholic fatty liver
- Sinusoidal obstruction syndrome
- Chronic hepatitis
- Nodular regeneration
- Vanishing bile duct syndrome
- Cirrhosis

DILI is one of the most common reason for unknown cause liver injury/liver disease
### DILI in Different Countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Sweden</th>
<th>Spain*</th>
<th>United States (DILIN)</th>
<th>Korea</th>
<th>Japan</th>
<th>Singapore</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>784</td>
<td>603</td>
<td>300</td>
<td>371</td>
<td>1676</td>
<td>31</td>
</tr>
<tr>
<td>Case ascertainment</td>
<td>Government registry</td>
<td>45 centers</td>
<td>Prospective, 5 centers</td>
<td>Prospective, 17 centers</td>
<td>Retrospective, multicenter</td>
<td>Prospective, population-based</td>
</tr>
<tr>
<td>HC/mixed/cholestatic (%)</td>
<td>52/21/29</td>
<td>55/21/25</td>
<td>56/20/24</td>
<td>NA</td>
<td>59/20/21</td>
<td>74/6/19</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>58 (42-74)</td>
<td>54 (13-88)</td>
<td>48 ± 18</td>
<td>49.0 ± 14.5</td>
<td>55</td>
<td>51</td>
</tr>
<tr>
<td>Female (%)</td>
<td>57</td>
<td>49</td>
<td>60</td>
<td>63.3</td>
<td>57</td>
<td>45</td>
</tr>
<tr>
<td>Hospitalized (%)</td>
<td>NA</td>
<td>54</td>
<td>54</td>
<td>100</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Died or transplanted (%)</td>
<td>9.2</td>
<td>5.4</td>
<td>10.1</td>
<td>1.3</td>
<td>3.7</td>
<td>9.6</td>
</tr>
<tr>
<td>Chronic DILI (%)</td>
<td>NA</td>
<td>16.9</td>
<td>13.6</td>
<td>NA</td>
<td>8.4</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Most frequent agents (%)</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Antibiotics (27)</td>
<td>Antibiotics (39)</td>
<td>Antimicrobials (45.5)</td>
<td>Herbal drugs (27.5)</td>
<td>Antibiotics (14)</td>
<td>Traditional CM (54)</td>
<td></td>
</tr>
<tr>
<td>Disulfiram (3.4)</td>
<td>CNS agents (15)</td>
<td>CNS agents (15)</td>
<td>Prescription drugs (20.8)</td>
<td>CNS agents (10)</td>
<td>Prescription drug (26)</td>
<td></td>
</tr>
<tr>
<td>Carbamazepine (2.2)</td>
<td>Analgesics (11)</td>
<td>Analgesics (11)</td>
<td>Health and dietary supplements (13.7)</td>
<td>Analgesics (9.9)</td>
<td>Malay herb (16)</td>
<td></td>
</tr>
<tr>
<td>Lipid-lowering agents (1)</td>
<td>Lipid-lowering agents (5)</td>
<td>Immunomodulator (5.5)</td>
<td>Medicinal herbs or plants (9.4)</td>
<td>Chinese herbs (7.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Analgesics (5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Antihypertensives (5)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Antineoplastics (4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lipid-lowering agents (3.4)</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
DILI-R Research

A Retrospective Study on Drug Induced Liver Injury in China (DILI-R)

This study has been completed.

Sponsor:
Drug Induced Liver Disease Study Group

Collaborator:
Unimed Scientific Inc.

Information provided by (Responsible Party):
Drug Induced Liver Disease Study Group

ClinicalTrials.gov Identifier:
NCT02407964

First received: March 31, 2015
Last updated: October 24, 2016
Last verified: October 2016

Study Population:
- Hospitalized Patient during 2012-2014

303 hospitals nationwide which cover all 31 provinces in mainland China involved

29,687 DILI cases in total enrolled
DILI Incidence Among Hospitalized Patients

DILI incidence (‰) by geographic locations of China

DILI 3-year incidence: 1.75‰

unpublished data
Increasing DILI Incidence

Trend of DILI Incidence (‰) of China

unpublished data
DILI Incidence Higher in Non-tertiary Hospitals

DILI incidence (%‰) in tertiary and non-tertiary hospitals of China

Tertiary: 1.55
Non-tertiary: 6.13

P < 0.001

unpublished data
Top-10 Classes of Suspicious Drug in General Hospitals

- Anti-biotics (include anti-TB drug)
- Herbs
- Chinese patent drug
- Anti-tumor drug

unpublished data
Top-20 Suspicious Drugs

unpublished data
Compare with WM, DILI Latent period is longer for those who Take TCM

P < 0.001

unpublished data
40% DILI Patients Take at Least 2 Suspicious Drugs
Live Injury Types

- Hepatocellular injury: 31.74%
- Cholestatic injury: 30.89%
- Mixed injury: 30.47%
- Unsure: 6.90%

unpublished data
At Baseline, ALT Above 10xULN Among 30% Patients

unpublished data
30% patients meet criteria of Hy's Law

Percentage of Hepatocyte injury type of DILI meeting Hy's Law criteria

- Yes: 30.92%
- No: 69.08%

About 3% patients progressed to liver failure or death

unpublished data
Liver Histology Presents Many Kinds of Liver Injury

<table>
<thead>
<tr>
<th>Liver histology characteristics</th>
<th>Cases and percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute hepatitis</td>
<td>438 (28.59%)</td>
</tr>
<tr>
<td>Chronic hepatitis</td>
<td>239 (15.60%)</td>
</tr>
<tr>
<td>Acute cholestasis</td>
<td>15 (0.98%)</td>
</tr>
<tr>
<td>Chronic cholestasis</td>
<td>10 (0.65%)</td>
</tr>
<tr>
<td>Cholestatic hepatitis</td>
<td>72 (4.70%)</td>
</tr>
<tr>
<td>Granulomatous change</td>
<td>3 (0.20%)</td>
</tr>
<tr>
<td>Macrosteatosis</td>
<td>9 (0.59%)</td>
</tr>
<tr>
<td>Microsteatosis</td>
<td>10 (0.65%)</td>
</tr>
<tr>
<td>NASH</td>
<td>17 (1.11%)</td>
</tr>
<tr>
<td>Coagulation/fusion necrosis</td>
<td>3 (0.20%)</td>
</tr>
<tr>
<td>Non focal necrosis</td>
<td>1 (0.07%)</td>
</tr>
<tr>
<td>Hepatocyte change</td>
<td>44 (2.87%)</td>
</tr>
<tr>
<td>Mixed or miscellaneous liver injury</td>
<td>3 (0.20%)</td>
</tr>
<tr>
<td>Slight nonspecific change</td>
<td>57 (3.72%)</td>
</tr>
<tr>
<td>Absolutely normal</td>
<td>4 (0.26%)</td>
</tr>
<tr>
<td>Massive necrosis</td>
<td>2 (0.13%)</td>
</tr>
<tr>
<td>Other</td>
<td>392 (25.59%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>219 (14.30%)</td>
</tr>
</tbody>
</table>

Among 1532 cases, Chronic DILI are 16.25%
Efficacy and Safety Study of Magnesium Isoglycyrrhizinate Injection in Subjects With Acute Drug-induced Liver Injury

This study has been completed.

Sponsor:
Chia Tai Tianqing Pharmaceutical Group Co., Ltd.

Information provided by (Responsible Party):
Chia Tai Tianqing Pharmaceutical Group Co., Ltd.

ClinicalTrials.gov Identifier:
NCT02734966

First received: April 6, 2016
Last updated: September 25, 2016
Last verified: September 2016
History of Changes
Magnesium Iso-glycyrrhizinate (MgIG) in The Treatment of Subjects with DILI

216 DILI patients

- Low dose 100mg/d (N=72)
- High dose 200mg/d (N=72)
- Tiopronin 100mg/d (N=72)

Primary endpoint:
ALT normalization at weeks 4

Randomized, double-blind, multi-doses, active drug controlled, multi-center study
Study Subjects

193 subjects screened, 19 subjects whose ALT<2xULN excluded

174 subjects enrolled and randomized into the trial

59 subjects in group A, the low-dose study group
- 54 subjects completed the trial
  - 5 subjects did not complete: 1 not effective, 4 withdrew informed consent

59 subjects in group B, the active comparator group
- 47 subjects completed the trial
  - 12 subjects did not complete: 6 not effective, 4 withdrew informed consent, 1 died, 1 adverse event

56 subjects in group C, the high-dose study group
- 54 subjects completed the trial
  - 2 subjects did not complete: 1 not effective, 1 withdrew informed consent
Rates of ALT Normalization At Weeks 1-4

Group A: low dose study drug; Group C: high dose study drug; Group B: active control

P < 0.001 at Week 2, 3 and 4

unpublished data
Rates of ALT Normalization At Weeks 1-4 for Subjects Who Stopped Suspicious Drug

P < 0.001 at Week 3 and 4

unpublished data
Rates of ALT Normalization At Weeks 1-4 for Subjects Who Cont' with Suspicious Drug

P < 0.001 at Week 2, 3 and 4

unpublished data
MgIG Approved of the Indication To Treat Acute DILI

The only drug approved of DILI indication globally
Translational Research Between Basic and Clinical

Anti-inflammatory Activity of Magnesium Isoglycyrrhizinate Through Inhibition of Phospholipase A2/Arachidonic Acid Pathway

Chunfeng Xie,¹ Xiaoting Li,¹ Jieshu Wu,¹ Zhaofeng Liang,¹ Feifei Deng,¹ Wei Xie,¹ Mingming Zhu,¹ Jianyun Zhu,¹ Weiwei Zhu,¹ Shanshan Geng,¹ and Caiyun Zhong¹,²

Basic Study

Magnesium isoglycyrrhizinate inhibits inflammatory response through STAT3 pathway to protect remnant liver function

Guang-Hua Tang, Hua-Yu Yang, Jin-Chun Zhang, Jin-Jun Ren, Xin-Ting Sang, Xin Lu, Shou-Xian Zhong, Yi-Lei Mao
**Anti-inflammation Mechanism of MgIG**

Dose dependently inhibit 3 major Inflammatory pathway:

- PLA2/AA signal channel
- NF-κB signal channel
- MAPK/AP-1 signal channel
Toxicity of novel anti-hepatitis drug bicyclol: A preclinical study

Geng-Tao Liu, Yan Li, Huai-Ling Wei, Hong Lu, Hui Zhang, Yu-Gui Gao, Ling-Zhi Wang

<table>
<thead>
<tr>
<th>Group</th>
<th>ALT (U/dl serum)</th>
<th>AST (U/dl serum)</th>
<th>Liver histopathology score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>23 ± 3.5</td>
<td>116 ± 21</td>
<td>0.33 ± 0.42*</td>
</tr>
<tr>
<td>CCl₄</td>
<td>658 ± 94</td>
<td>488 ± 86</td>
<td>4.15 ± 1.99</td>
</tr>
<tr>
<td>CCl₄+Bicyclol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 mg/kg (× 2)</td>
<td>353 ± 186*</td>
<td>397 ± 123</td>
<td>NE</td>
</tr>
<tr>
<td>100 mg/kg (× 2)</td>
<td>353 ± 191*</td>
<td>342 ± 117</td>
<td>NE</td>
</tr>
<tr>
<td>200 mg/kg (× 2)</td>
<td>71 ± 18*</td>
<td>250 ± 49*</td>
<td>1.40 ± 0.13†</td>
</tr>
<tr>
<td>CCl₄+DDA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 mg/kg (× 2)</td>
<td>627 ± 162</td>
<td>529 ± 134</td>
<td>NE</td>
</tr>
<tr>
<td>100 mg/kg (× 2)</td>
<td>600 ± 125</td>
<td>517 ± 59</td>
<td>NE</td>
</tr>
<tr>
<td>200 mg/kg (× 2)</td>
<td>407 ± 197†</td>
<td>486 ± 133</td>
<td>3.03 ± 1.53</td>
</tr>
</tbody>
</table>

n = 10 per group. *P<0.01, †P<0.05 vs. CCl₄. NE, not examined; DDA, dimethoxy dicarboxylate biphenyl; ALT, alanine aminotransferase; AST, aspartate aminotransferase.
Bicyclol Inhibit expression and activity of inflammatory cytokines

NF-κB

** P<0.01

TNF-α

* P<0.05

IL-1β

*** P<0.001

TGF-β₁

* P<0.05


RCT Study on Bicyclol to Treat DILI Has Been Initiated

A Multicenter, Randomized, Double-blind Clinical Trial Was Conducted to Evaluate the Efficacy and Safety of Bicyclol in the Treatment of Acute Drug-induced Liver Injury and to Screen Biomarkers for Prognosis

This study is currently recruiting participants. (see Contacts and Locations)
Verified October 2016 by Drug Induced Liver Disease Study Group
Sponsor:
Drug Induced Liver Disease Study Group

ClinicalTrials.gov Identifier:
NCT02944552
First received: October 24, 2016
Last updated: October 25, 2016
Last verified: October 2016
History of Changes

Information provided by (Responsible Party):
Drug Induced Liver Disease Study Group
Prospective Research Is Ongoing

A Prospective Cohort Study on Drug-induced Liver Injury in China (DILI-P) (DILI-P)

This study is currently recruiting participants. (see Contacts and Locations)
Verified November 2016 by Drug Induced Liver Disease Study Group

Sponsor:
Drug Induced Liver Disease Study Group

Information provided by (Responsible Party):
Drug Induced Liver Disease Study Group

ClinicalTrials.gov Identifier:
NCT02961413
First received: October 24, 2016
Last updated: December 19, 2016
Last verified: November 2016

- More than 100 hospitals involved
- Follow up at least 6 month
- Collect clinical information
- Set up sample bank
- Biomarker research
A Professional DILI Platform in China: HepaTox
Released The First DILI Clinical Guideline in China
The Future Outlook To DILI
Translational Research

- **Diagnosis**
  - Confirm normal ALT
  - Develop new method for causality assessment

- **Pathogenesis**
  - Idiosyncratic animal model
  - Host, drug and environmental

- **Risk factors**
  - Host, drug and environmental

- **Biomarkers**
  - Diagnosis
  - Tolerators, adaptors, susceptibles
  - Prognosis

- **Treatment**

Regional/Global cooperation is needed
Thank you for your attention!

www.hepatox.org