ILC 2019 - Toxic and alcoholic liver injury

ד"ר מייכל כהן
איילת 2019
Cause of Toxic Hepatitis

Irritant toxins to liver cells are alcohol, chemicals, street drugs and some nutritional supplements.
Metamizole as a leading cause of drug-induced liver injury
Marcial Sebode et al, Hamburg, Germany

- In US - Metamizole or Dipyrone is banned from the market - but is approved and frequently applied in other countries

- Large multicenter US DILI registries have identified the antibiotics such as amoxicillin-clavulonate and analgetics as most frequent agents causing DILI

- Elevation of liver enzymes is not listed as a potential side effect on the label of metamizole in Germany (and in Israel)
Aim & Methods

• **Aim**
  - To determined the *frequency* and *pattern* of metamizole-induced DILI at tertiary care center in Germany

• **Method**
  - Retrospective study
  - Consecutive DILI cases admitted to the Internal department of Medicine at the University Medical Centre Hamburg-Eppendorf
  - Cases of acute hepatitis other than DILI were exclude
Results

• 154 DILI cases with acute hepatitis were admitted 2008 to 2017

• Metamizole was the **second most** frequent putative agent causing DILI (23, 14.9%)
  – 14 cases - metamizole was the only drug
  – 9 cases had concomitant medication potential like statins or NSAIDs
  – 4 patients were re-challenged, resulting in another episode of acute icteric hepatitis
Results

• The biochemical pattern was hepatocellular with median levels of ALT (823 U/l)
• 61% - ANA and/or anti-SMA
• 15/23 (65%) had liver biopsy
  – The histological pattern - acute hepatitis with infiltrating lymphocytes, centrilobular necrosis but no interface hepatitis
Treatment and Summary

• **Treatment**
  • 68% - treated with steroids
  • In 21 / 23 - liver damage resolved
  • 2 patients - received liver transplantation

• **Conclusion**
  • Acute hepatitis or acute liver failure are not mentioned in the German label of metamizole or dipyrone as side effects
  • Metamizole is a frequent and underrated agent causing DILI, and can lead to acute liver failure
Herbal medicines induces severe liver injury than western medications: A nationwide multicenter retrospective research

Jun Chen et al, China DILI group

- Herbal medicines (HM) are widely

- This study aims to investigate the differences between HM DILI and western medications (WM) DILI
Method

- Multicenter retrospective study

- 29,478 DILI patients hospitalized from January 1, 2012 to December 31, 2014

- Patients who took either HM or WM with RUCAM scores are more than 6 were analyzed
Results

• 3711 HM and 8859 WM cases were enrolled
Agents
Acute liver Failure and Liver Related Death were Higher in the HM group and WM group
האמ כעליה באנזימי כל בחלולה המטوفת תרופית
קשור לתרופה?
Liver enzyme elevations and hepatotoxicity in patients treated with checkpoint inhibitor immunotherapy

Morven Cunningham, Toronto Canada

- Liver immune-related adverse events (LirAE) frequently occur with Checkpoint inhibitors (CPI) therapy

- **Aim:** To better understand the causes of liver enzyme elevation (LEE), frequency of LirAEs and the resulting impact on patient management
Methods

• All Patients from Phase I/II clinical trials (Tumor Immunotherapy Program) with clinically significant LEE (ALT/AST > 3xULN and/or bilirubin > 1.5xULN) enrolled

• Clinical records reviewed for cause, investigation, management and clinical outcomes
# Results

## Patient demographics

<table>
<thead>
<tr>
<th>Therapy type</th>
<th>Patients (%) treated with CPi (N=472)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-PD-1</td>
<td>65.2</td>
</tr>
<tr>
<td>Combination CPi</td>
<td>6.1</td>
</tr>
</tbody>
</table>

## Clinically significant LEE

<table>
<thead>
<tr>
<th>Diagnostic evaluation</th>
<th></th>
</tr>
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<tbody>
<tr>
<td>Liver imaging</td>
<td>71.6</td>
</tr>
<tr>
<td>HBV/HCV serology</td>
<td>16.7</td>
</tr>
<tr>
<td>Autoimmune serology</td>
<td>13.7</td>
</tr>
<tr>
<td>Liver biopsy</td>
<td>2.9</td>
</tr>
</tbody>
</table>

## LEE attributed to

| Disease progression                | 54.9 |
| Other drugs/toxins                | 6.9  |
| Surgery                            | 4.9  |
| Other                              | 16.7 |
| LirAE                              | 16.7 of LEE (3.6% of total cohort) |
Results

• LirAE associated with
  – Prior CPi exposure (in 41.2% of patients with vs. 15.4% without LirAE; p=0.011)
  – Other irAEs (in 76.5% of patients with vs. 19.2% without LirAE; p=<0.001)

• 15/17 patients with LirAE received steroids and liver enzymes normalized after a median of 37 days (IQR 21–52)

• 4 patients received further CPi
  – 1 had recurrent LirAE
## Follow Up

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients (N=472)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up, median (IQR)</td>
<td>7.5 months (3.6–16.2)</td>
</tr>
<tr>
<td>Total disease progression, n (%)</td>
<td></td>
</tr>
<tr>
<td>Patients with LirAE (%)</td>
<td>421 (89.2)</td>
</tr>
<tr>
<td>Patients without (%)</td>
<td>52.9 86.7</td>
</tr>
<tr>
<td>Death, n (%)</td>
<td>292 (61.9)</td>
</tr>
<tr>
<td>Death due to complications from LirAE</td>
<td>0</td>
</tr>
</tbody>
</table>

\[ p=0.001 \]
Conclusion

• Liver enzymes elevated are common in patients receiving Cpi may be unrelated to Cpi requiring a full diagnostic evaluation
אופזיה סיפוליית
לפיגיעה תוקסיתخشא?
Calmangafodipir (trial drug PP100-01) is a superoxide dismutase mimetic that prevents APAP toxicity in mice.

The POP Trial - phase 1, open label, randomised study of PP100-01 co-treatment with N-acetylcysteine (NAC) regimen in APAP overdose.
Methods

- 24 patients recruits during 2017-18

- The inclusion criterion were:
  - adults within 24 h of a single or staggered APAP overdose that required NAC treatment
  - one of 3 sequential dosing cohorts (NAC+ PP100-01 2,5 and 10μmol/kg vs NAC)
  - Participants, study and clinical teams were not blinded

- The primary outcome was the safety and tolerability of PP100-01

- Secondary outcomes - biomarkers
  - alanine transaminase (ALT) activity, full-length keratin-18, microRNA-122 (miR-122)
Results

• Serious adverse event (SAE) were:
  – NAC alone 2/6 patients
  – NAC +PP100-01 (2μmol/kg) 4/6 patients
  – NAC+PP100-01 (5μmol/kg) 2/6 patients
  – NAC +PP100-01 (10μmol/kg) 3/6 patients

• There were no AEs or SAEs probably or definitely related to PP100-01
Biomarker showed Reduction in Liver Injury

- No treatment group had an increase in ALT

- miR-122 was similar to FLK18.
Conclusion

• PP100-01 was tolerated in patients treated with NAC

• In APAP overdose may reduce liver injury
מראות פרגונסטיים?
The association between liver type fatty acid binding protein (FABP1) serum levels and clinical outcomes in patients with non-acetaminophen acute liver failure: A cohort study
Constantine Karvellas, Canada

• Acute liver failure (ALF) is associated with significant mortality

• FABP1 demonstrated to improve prognostic discrimination in acetaminophen (APAP)-induced ALF

• **The aim** - to determine serial FABP1 levels (early or late) are associated with 21-day transplant-free survival in non-APAP ALF
Results

• 384 patients with ALF included
  – Autoimmune hepatitis (AIH, n = 125)
  – drug-induced liver injury (DILI, n = 141)
  – Hepatitis B (n = 118)

• Overall
  – 177 (46%) ALF patients received LT
  – 88 Transplant-free survivors
Results

• **Biochemically**
  – FABP1 levels were significantly lower in TFS patients at day 3–5 (TFS 54 vs. NTFS 66ng/ml; p = 0.049)
  – but not admission
    (TFS 96 vs. NTFS 87 ng/ml; p = 0.67)

• **Clinically**
  • Transplant-free survivors required less:
    – mechanical ventilation (21 vs. 66%)
    – vasopressors (10% vs. 35%)
    – Grade III/IV hepatic encephalopathy (30% vs. 73%, p < 0.0001)
Summary

• Increased FABP1 levels at late time points (day 3–5) were significantly associated with worse outcomes (death/LT) in AIH, HBV and DILI

FABP1 may potentially help identify ALF patients with higher recovery potential at later time points
Baseline neutrophil-to-lymphocyte ratio indicates infection and acute kidney injury, and is related to corticosteroid Lille response in alcoholic hepatitis

Ewan Forrest, UK

• To assess the Neutrophil-to-lymphocyte ratio (NLR) which reflect sepsis and inflammation in the prognosis of alcoholic hepatitis

• NLR calculated from 789 patients in the STOPAH trial
  – Infection episode
  – Prevalent and incidence of AKI
Results

• NLR was higher in patients with AKI or infection

<table>
<thead>
<tr>
<th></th>
<th>NLR</th>
<th>p</th>
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<tbody>
<tr>
<td><strong>Incident AKI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present (n=67)</td>
<td>7.5 (6.4, 8.7)</td>
<td>0.0056</td>
</tr>
<tr>
<td>Absent (n=403)</td>
<td>6.0 (5.6, 6.4)</td>
<td></td>
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<tr>
<td><strong>Infection by Day 7</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present (n=94)</td>
<td>7.8 (6.3, 9.2)</td>
<td>0.035</td>
</tr>
<tr>
<td>Absent (n=695)</td>
<td>6.1 (5.8, 6.5)</td>
<td></td>
</tr>
<tr>
<td><strong>Infection by Day 28</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present (n=185)</td>
<td>7.1 (6.3, 8.0)</td>
<td>0.025</td>
</tr>
<tr>
<td>Absent (n=604)</td>
<td>6.1 (5.6, 6.5)</td>
<td></td>
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</tbody>
</table>
Lille Response to Prednisolone treatment was more likely if NLR ≥5

CONCLUSIONS: A Lille response to prednisolone is more likely if NLR ≥5, but development of infection or AKI after prednisolone treatment is greater if NLR >8

Risk of developing infection and AKI after prednisolone treatment greater if NLR >8 vs ≤8
Thank You
Baseline neutrophil-to-lymphocyte ratio indicates infection and acute kidney injury, and is related to corticosteroid Lille response in alcoholic hepatitis.

**RESULTS (Cont.)**

- Risk of developing infection and incident AKI after prednisolone treatment greater if NLR >8 vs ≤8:
  - Infection by Day 7: 17.3% vs 7.4%: p=0.006; OR 2.60
  - Infection by Day 28: 30.6% vs 20.0%: p=0.031; OR 1.76
  - Incident AKI: 20.8% vs 7.0%: p=0.008; OR 3.46

**TABLE**

<table>
<thead>
<tr>
<th>NLR &lt;5</th>
<th>NLR ≥5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisolone</td>
<td>63.7%</td>
</tr>
<tr>
<td>Untreated</td>
<td>64.5%</td>
</tr>
</tbody>
</table>

**CONCLUSIONS** High NLR associates with prevalent AKI and infection in alcoholic hepatitis. A Lille response to prednisolone is more likely if NLR ≥5, but development of infection or AKI after prednisolone treatment is...
Herbal Medicines Induces More Severe Liver Injury than Western Medications: Data from a nationwide multicenter retrospective research

Jun Chen, Xinyu Liu, Rongtao Lai, Yimin Mao, Chengwei Chen, China DILI Study Group

INTRODUCTION

Drug-induced liver injury (DILI) is defined as the liver injury attributable to medications, traditional Chinese medicines (TCM), herbal medicines, or herbal remedies. In western countries, the most common cause of DILI is medications; however, in Asian patients, herbal medicines (HM) is often the primary cause of DILI. Only few studies regarding the causes, clinical features, and outcomes of HM-induced liver injury in a large population are available.

AIM

We performed a three-year nationwide multicenter retrospective study to investigate the characteristics of HM-causing DILI and intensively investigate the differences between HM-induced DILI (HM-DILI) and western medications (WM)-induced DILI (WM-DILI).

METHOD

We collected data from a total of 1279 confirmed DILI cases hospitalized from Jan. 1st, 2012 to Dec. 31st, 2014 in 208 medical centers in major cities across mainland China. The eligible patients were divided into two groups according to causative agent: herbs medicines (HM) group and western medications (WM) group. The data on demographics, clinical characteristics, associated drugs, and outcomes of DILI patients were collected and systematically evaluated.

RESULTS

A total of 371 HM and 908 WM cases were enrolled in the study. The mean age of the HM group was 49.6 ± 1.46 years, and that of the WM group was 44.2 ± 1.78 years (P=0.001). Females (63.0%) were predominant in the HM group. The median of serum level of ALT, AST, ALP, TBL, and DILI at baseline and peak value were significantly higher in the HM group (P<0.001). Although the general mortality of the two groups did not differ significantly (P=0.19), the liver-related death varied significantly (P=0.025). The 7-day mortality of the HM group was 5.3% versus 0.2% in the WM group (5.3%/0.2%/P=0.001). The incidence of liver cancer was 1%, and chronic liver failure, and chronic DILI was more frequent in the HM than the WM group (5.3%/0.6%/ vs. 1.5%/1.2% vs. 0.8%/0.8%/P=0.05).

Table 1. Demographic and clinical characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HM (n=76)</th>
<th>WM (n=603)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>49.6±1.46</td>
<td>44.2±1.78</td>
</tr>
<tr>
<td>Sex</td>
<td>50 (64.9)</td>
<td>281 (46.5)</td>
</tr>
<tr>
<td>Gender (%male)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>5.3%</td>
<td>0.2%</td>
</tr>
</tbody>
</table>

CONCLUSIONS

- We have presented the most extensive characterization of herbal medicine DILI in China to date.
- HM-DILI is more common in older individuals and women.
- HA-DILI may cause more severe liver injury with worse outcomes than WM-DILI. The concept that herbs are safe and innocuous needs to be changed. The hepatotoxicity of herbal medicines should never be neglected.

REFERENCES


ACKNOWLEDGMENTS

We greatly appreciate all participants from 208 medical centers for data collection. Dr. Han Kain for statistical analysis.

CONTACT INFORMATION

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Email: chenjun36@126.com
Metamizole as a leading cause of drug-induced liver injury (DILI)

INTRODUCTION & OBJECTIVES
Drug-induced liver injury (DILI) is a heterogeneous entity leading to acute liver damage (1,2). Large DILI registries like in the United States have identified the most frequent agents causing DILI, among those being primarily antibiotics such as amoxicillin-clavulanate or analgetics (3). We have analysed the most frequent drugs causing DILI at our tertiary care centre.

RESULTS
154 DILI cases with acute icteric hepatitis were admitted to our centre from 2008 to 2017. After phenprocoumon, metamizole was identified as the second most frequent drug causing DILI (14.9% of all DILI cases). The clinical characteristics of patients with metamizole-induced liver injury are shown in Table 1. Liver biopsy was performed for the majority of patients with metamizole-induced DILI (see for an example Figure 1). Infiltration of immune cells and centrilobular damage with variable degree of necrosis were the most frequent histopathological characteristics (Table 2).

METHODS
Consecutive cases of DILI presented to the I. Department of Medicine at the University Medical Centre Hamburg-Eppendorf were analysed retrospectively. Causality was assessed by the RUCAM score. Cases of acute hepatitis other than DILI were excluded, especially acute hepatitis E viral infection. Autoimmune hepatitis (AIH) was ruled out by clinical follow-up of DILI cases to assure that liver enzymes did not rise again after the drug had been stopped.

CONCLUSIONS

Table 1) Clinical characteristics of metamizole-induced DILI

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Age (Years)</th>
<th>Sex</th>
<th>Follow-up (Months)</th>
<th>RUCAM</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>23</td>
<td>40 (26-79)</td>
<td>Female</td>
<td>4.5</td>
<td>8 (5-11)</td>
</tr>
<tr>
<td>Recovery</td>
<td>21</td>
<td>40 (26-79)</td>
<td>Female</td>
<td>4.5</td>
<td>8 (5-11)</td>
</tr>
<tr>
<td>ALF+LTX*</td>
<td>2</td>
<td>50 (33-67)</td>
<td>Male</td>
<td>1 (before LTX)</td>
<td>8 (7-8)</td>
</tr>
</tbody>
</table>

Table 2) Histological characteristics of metamizole-induced DILI

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Liver biopsy</th>
<th>Inflammatory activity</th>
<th>Cholestasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>23</td>
<td>17/23 (73.9%)</td>
<td>Mild</td>
<td>2/17 (11.8%)</td>
</tr>
<tr>
<td>Recovery</td>
<td>21</td>
<td>15/21 (71.4%)</td>
<td>Mild</td>
<td>2/15 (13.3%)</td>
</tr>
<tr>
<td>ALF+LTX*</td>
<td>2</td>
<td>2/2 (100%)</td>
<td>Mild</td>
<td>0/2 (0%)</td>
</tr>
</tbody>
</table>

*ALF+LTX, acute liver failure and consecutive liver transplantation

Figure 1) Liver biopsy of metamizole-induced DILI