Incidence rate of liver injury in pediatric population: data mining on electronic healthcare databases in Europe

Carmen Ferrajolo, Katia MC Verhamme, Annalisa Capuano, Gianluca Trifirò, Geert W 't Jong, Alessandro Oteri, Gino Picelli, Giampiero Mazzaglia, Claudio Cricelli, Francesco Rossi and Miriam CJM Sturkenboom

Dpt. of Experimental Medicine, Second University of Naples; Italy
Dpt. of Medical Informatics, Erasmus University Medical Center, the Netherlands
Disclosure of conflicts of interest

MS is heading a research group that occasionally conducts research for pharmaceutical companies under strict conditions regarding IP and publication rights.

This study was not funded, no conflicts to report.
Background - 1

Drug induced liver injury (DILI):

- leading cause of acute liver failure in the US
  
  *(Lee WM et al. Seminar Liver Dis 2003)*

- under-recognized cause of less severe liver injury worldwide
  
  *(Navarro et al. NEJM 2006)*

- leading reason for drug withdrawal from the market
  
  *(Temple et al. JAMA 2002)*

- overall incidence rate in general population is roughly 14 per 100,000 patient years
  
  *(Sgro et al. Hepatology 2002)*
Background - 2

- Lack of population-based data in pediatrics
- Important differences with respect to adults
  - Risk factors
  - Drug prescription patterns
  - Susceptibility
Spontaneous reporting systems and DILI in children

Based on WHO Vigibase data:

- DILI is infrequently reported as suspected ADR in children and adolescents (1%)

- Reported ADRs for DILI in children regard the same drugs as in adults (acetaminophen, antiepileptic and anti-tuberculosis)

Ferrajolo et al, Br J Clin Pharmacol 2010
Objectives

1. Estimate the incidence rate of liver injury in the pediatric general population

2. Detect associations between drug use and liver injury based on electronic healthcare data
### Data sources: electronic medical record DBs

<table>
<thead>
<tr>
<th>Country</th>
<th>Data Source</th>
<th>Participants</th>
<th>Start of Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ITALY</strong></td>
<td>Pedianet</td>
<td>300 pediatricians</td>
<td>1998</td>
</tr>
<tr>
<td></td>
<td></td>
<td>145,706 children (0-14)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Health Search/Thales</td>
<td>650 GPs</td>
<td>1998</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>63,300</strong> pediatric patients (14-17)</td>
<td></td>
</tr>
<tr>
<td><strong>the Netherlands</strong></td>
<td>Integrated Primary Care Information</td>
<td>400 GPs</td>
<td>1998</td>
</tr>
<tr>
<td></td>
<td></td>
<td>93,307 pediatric patients (0-17)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Start of Follow-up 1996</td>
<td></td>
</tr>
</tbody>
</table>

**Health Search/Thales**

- 650 GPs
- **63,300** pediatric patients (14-17)
- Start of Follow-up: 1998
Methods

**Design:** Cohort study

**Study period:** Jan 2001 – Dec 2008

**Study population:** children and adolescents (< 18) with at least six months of follow-up

**Exclusion criteria:** prevalent liver injury at the study entry

**End of follow-up:** a) liver injury diagnosis; b) death; c) transferring out of the practice; d) end of study period
Study outcome: Idiopathic Liver Injury (ILI)

- Exclusion of liver injury due to other causes: infections, alcohol, autoimmune and metabolic disorders, biliary diseases, abdominal trauma or neonatal hepatitis (Graham D et al, Am J Gastroenterol. 2003)

- Potentially drug-induced liver injury
Case definition: Idiopathic Liver Injury

• abnormal liver enzymes
  – ALT OR AST OR ALP OR TB (only with any elevation of ALT, AST or ALP) >2xULN
  OR
  Diagnosis of:
  • hepatitis
  • hepatic necrosis
  • steatosis (or fatty liver)
  • hepatophaty
  • jaundice*
  • hepatomegaly*

* only with any elevation of liver enzymes
**Case ascertainment**

1. Broad selection through codes (ICPC e ICD9), free text and lab data
2. Manual review of electronic medical records (blinded to the exposure)
3. Doubtful cases reviewed by MDs to reach consensus

- **Isolated hepatomegaly**
- **Definite case**
  - diagnosis confirmed by
    - Specialist
    - lab data
    - GP/FP (only with details)
- **Possibile case**
  - in case GP/FP considers diagnosis of liver injury
Data analysis: distributed data model and Jerboa

- Age standardized incidence rates (WHO World Standard population)

- Associations between drug use and ILI: based on incidence rate ratios adjusted for age and sex (EU-ADR)

Copyright EU-ADR: http://www.euadr-project.org/
Age-standardized incidence rate of ILI by gender and country

![Bar chart showing the age-standardized incidence rate of ILI by gender and country, with Italy and the Netherlands compared. The chart includes the incidence rates per 100,000 PYs for both male and female populations.](chart.png)
Incidence rate of ILI by age category and country

IR of ILI increases consistently with age
Incidence rate of ILI (including isolated hepatomegaly) by age category and country
Case characteristics (only definite cases)

Italy (HSD+Pedianet = 731) vs the Netherlands (IPCI = 54)

- **Hepatitis**: 69% in Italy, 46% in the Netherlands
- **More than 1 sign**: 17% in Italy, 48% in the Netherlands
- **Steatosis**: 5% in Italy, 6% in the Netherlands
- **Abnormal liver enzymes**: 9% in Italy, 6% in the Netherlands

Additional symptoms:
- Italy: hepatitis, more than 1 sign, steatosis, abnormal liver enzymes
- Netherlands: hepatitis, more than 1 sign, steatosis, abnormal liver enzymes
<table>
<thead>
<tr>
<th>Drugs</th>
<th>Exposure (in-days)</th>
<th>No. of events (tot=110)</th>
<th>IRR CI% 95</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin and enzyme inhibitor</td>
<td>437708</td>
<td>16</td>
<td>18.6 (11.3-30.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>156763</td>
<td>9</td>
<td>25.9 (13.4-50.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>759972</td>
<td>6</td>
<td>7.5 (3.4-16.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>Rifampicin and isoniazid</td>
<td>114</td>
<td>2</td>
<td>4858.2 (1214.0-19442.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>Paracetamol, combinations</td>
<td>9740</td>
<td>2</td>
<td>94.2 (23.4-378.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Rokitamycin</td>
<td>13329</td>
<td>2</td>
<td>52.3 (13.0-209.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Sulfamethoxazole and trimethoprim</td>
<td>42325</td>
<td>2</td>
<td>28.6 (7.1-114.7)</td>
<td>0.002</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>23337</td>
<td>2</td>
<td>25.8 (6.4-103.4)</td>
<td>0.003</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>49585</td>
<td>2</td>
<td>11.1 (2.8-44.5)</td>
<td>0.015</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>76355</td>
<td>2</td>
<td>9.5 (2.4-38.2)</td>
<td>0.019</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>134725</td>
<td>2</td>
<td>6.9 (1.7-27.6)</td>
<td>0.035</td>
</tr>
</tbody>
</table>
Limitations

Incidence rate of ILI

• Diagnostic bias across country

Signal detection: drugs and ILI

• Hypothesis generation analysis
• No causality assessment for found associations
• Most of confounders have not been controlled

Case-control analysis is ongoing
Conclusions

- Incidence rate of Idiopathic Liver Injury in the pediatric population differ by country and age

- Difference in access to healthcare resources may partly account for observed differences between Italy and the Netherlands

- Using signal detection techniques, drug classes that are associated with ILI are known hepatotoxic drugs in adults: antibiotics, rifampicin/isoniazid, anti-epileptics
Thanks!

c.ferrajolo@erasmusmc.nl
carmen.ferrajolo@unina2.it