ASSOCIATION BETWEEN USE OF ASTHMA DRUGS IN CHILDREN AND LIVER INJURY

CARMEN FERRAJOLO, MARJOLEIN ENGELS, KATIA VERHAMME, CARLO GIAQUINTO, CLAUDIO CRICELLI, GIANLUCA TRIFIRÒ, ANNALISA CAPUANO, AND MIRIAM STURKENBOOM

CAMPANIA REGIONAL CENTRE OF PHARMACOVIGILANCE AND PHARMACOEPIDEMIOLOGY
EXPERIMENTAL MEDICINE DEPARTMENT, PHARMACOLOGY DIVISION, SECOND UNIVERSITY OF NAPLES; ITALY

DPT. MEDICAL INFORMATICS, ERASMUS UNIVERSITY MEDICAL CENTER, ROTTERDAM; THE NETHERLANDS
Asthma is the most common chronic airway disease among children and first symptoms occur at around 5 years.  

US: >10 million children under age 18 (14%) ever suffered asthma ATTACK; 6.8 million children still have chronic asthma (9%).

Asthma is characterized by two components, either inflammatory or functional alteration, thus it requires a dual treatment, including steroids and/or bronchodilators.
GLOBAL INITIATIVE FOR ASTHMA (GINA 2010) GUIDELINES IN CHILDREN

SABA & LABA: $\beta_2$ adrenergic agonists (short-term and long term acting)

ICS: Inhaled corticosteroids

LTRA: Leukotriene receptor antagonists
INHALED MEDICINES AND SYSTEMIC ABSORPTION

- >10 µm: mouth
- <0.5 µm: exhaled
- 1-5 µm: small airways

Lung deposition (10% to 30%)

Swallowed fraction (70% to 90%)

Absorption from the gut

Active drug from the gut (B)

Systemic circulation

Absorption from the lung (A)

GI tract

Liver

Inactivation in the liver "first pass"
LEUKOTRIENES RECEPTORS ANTAGONISTS (LTRA)
- mild, asymptomatic ALT elevations occur in 1.5% of patients receiving zafirlukast;
- Rarely severe hepatic failure, resulting in liver transplantation or death;
- Onset typically within 2 to 6 months of starting therapy;
- One case of montelukast-induced liver toxicity in children¹.

B₂-ADRENERGIC AGONISTS
- ALT elevations occur in less than 1% of patients;
- After long term oral therapy with B₂-adrenergic bronchodilators.

CORTICOSTEROIDS (CS)
- Oral CS have been reported to be associated with liver toxicity, while inhaled CS are thought to be much lower associated than orally intake.

# SIGNAL DETECTION IN EU-ADR NETWORK

## Table 2. Comparison of different methods applied for signal detection concerning acute liver injury

<table>
<thead>
<tr>
<th>ATC</th>
<th>Drugs</th>
<th>No. of cases</th>
<th>Exposure (PYs)</th>
<th>Crude IR/10,000 PY (95% CI)</th>
<th>RR&lt;sub&gt;LGPS&lt;/sub&gt; (95% CI)</th>
<th>RR&lt;sub&gt;SCCS&lt;/sub&gt; (95% CI)</th>
<th>LEOPARD*</th>
</tr>
</thead>
<tbody>
<tr>
<td>A02</td>
<td>Ranitidine</td>
<td>7</td>
<td>3,833.86</td>
<td>18.3 (8.14-35.8)</td>
<td>43.7 (17.7-87.6)</td>
<td>12.9 (4.9-34.0)</td>
<td>yes</td>
</tr>
<tr>
<td></td>
<td>Omeprazole</td>
<td>7</td>
<td>5,583.97</td>
<td>12.5 (5.6-24.6)</td>
<td>29 (9.5-60.9)</td>
<td>13.3 (4.9-35.6)</td>
<td>yes</td>
</tr>
<tr>
<td></td>
<td>....</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R03</td>
<td>Flunisolide*</td>
<td>4</td>
<td>27,548.87</td>
<td>1.5 (0.5-34.5)</td>
<td>3.4 (1.3-7.6)</td>
<td>2.7 (0.9-8.1)</td>
<td>no</td>
</tr>
<tr>
<td>R06</td>
<td>Cetirizine</td>
<td>5</td>
<td>43,255.13</td>
<td>1.2 (0.4-2.5)</td>
<td>2.5 (1.0-5.1)</td>
<td>3.0 (1.2-7.7)</td>
<td>yes</td>
</tr>
</tbody>
</table>

Drugs with ≥3 exposed cases of ALI and a lower band of 95% CI of RR >1 when applying LGPS method.

*not statistically significant association when using SCCS method;

*Yes = propathic bias is likely to be present, No = propathic bias is unlikely to be present.
OBJECTIVE

By combining multiple healthcare databases from two EU Countries, we assessed the risk of liver injury associated with anti-asthma medications, as a whole class and by therapeutic classes and individual compounds, in children and adolescents outpatients.
METHODS

Design: Case-control analysis

Period: Jan 2001 – Dec 2008

Setting: General Practitioner and Family Pediatrician healthcare databases from Netherlands and Italy

Study population: Children and adolescents outpatients (<18 years)
POOLING OF ELECTRONIC MEDICAL RECORD DATABASES

- 300 Family Paediatricians (FP)
- 145,706 children (<14y)
- 400 GPs
- 93,307 children (<18y)
- 900 General Practitioners (GPs)
- 190,772 children (14-17 y) > 400,000 children
CASE OF LIVER INJURY ASCERTAINMENT

1. Initial broad case selection through search based on:
   a) terminology specific diagnostic codes (ICPC and ICD9) related to liver disease
   b) free text
   a) laboratory data (i.e. Alanine/Aspartate Amino Transferases, OR Alkaline phosphatase OR Total Bilirubin)

2. Manual review of all potential cases by medically trained researchers using common algorithm (blinded to the drug exposure)

EXCLUSION CRITERIA
- Liver injury due to other specified causes:
  - viral infections; alcohol abuse; autoimmune, or metabolic disorders or abdominal trauma
- Neonatal hepatitis
- Isolated jaundice and hepatomegaly
- Chronic liver disease
- Small elevation of liver tests (≤ 2xULN)

CASE
- diagnosis of liver injury by one of those:
  - Specialist;
  - GP/FP confirmed by diagnostic tests;
  - lab data (>2xULN)

3. Doubtful cases reviewed by two experts to reach consensus
SELECTION OF CONTROLS

• 100 controls for each case (incidence density sampling) matched by:
  – index date (date of case onset)
  – Age
  – Sex
  – Database
ANTI-ASTHMA DRUGS EXPOSURE DEFINITION

Prescriptions of any R03:
• β₂-adrenergic agonists short and long acting (SABA & LABA) and in combination;
• Inhaled and Oral corticosteroids (ICS and CS);
• Anticholinergics;
• Chromones;
• Theophyllines;
• Leukotriene receptor antagonists (LTRA).

Exposure categories based on regency of use:

- Current use
- Past use
- Distant use
- Recent use

365 days | 180 days | 30 days

Index Date
Date of newly diagnosed hepatotoxicity
Main analysis:

- By conditional logistic regression we measured the Crude OR (95% CI) as the probability to develop liver injury in children and adolescents with the use of class/individual anti-asthma drugs, as compared to no use of these medications.
- Adjusted OR for all covariates (P>0.10)

Sensitivity analyses:

- Restricted analysis among R03 users to control for confounding by indication
- Stratified the analyses by duration of the therapy
- Removal of carry-over period to explore the possible effect of misclassification of the exposure
## Characteristics of Cases and Controls

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
<th>Matching factor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Girls</td>
<td>392 (41.8)</td>
<td>39,106 (41.8)</td>
<td></td>
</tr>
<tr>
<td><strong>Age cat. (yrs)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2</td>
<td>88 (9.4)</td>
<td>8811 (9.4)</td>
<td>Matching factor</td>
</tr>
<tr>
<td>2-5</td>
<td>101 (10.8)</td>
<td>9704 (10.4)</td>
<td></td>
</tr>
<tr>
<td>6-11</td>
<td>260 (27.8)</td>
<td>26,060 (27.7)</td>
<td></td>
</tr>
<tr>
<td>12-18</td>
<td>489 (52.1)</td>
<td>49,090 (52.4)</td>
<td></td>
</tr>
<tr>
<td><strong>Database</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HSD</td>
<td>478 (51)</td>
<td>47,480 (51)</td>
<td></td>
</tr>
<tr>
<td>Pedianet</td>
<td>382 (40.7)</td>
<td>38,159 (40.7)</td>
<td></td>
</tr>
<tr>
<td>IPCI</td>
<td>78 (8.3)</td>
<td>7706 (8.2)</td>
<td></td>
</tr>
</tbody>
</table>
## Risk Factor

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Cases</th>
<th>Controls</th>
<th>OR* (95% CI)</th>
<th>p-value^</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>16 (1.7)</td>
<td>264 (0.3)</td>
<td>6.2 (3.7-10.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Obesity</td>
<td>57 (6.1)</td>
<td>1767 (1.9)</td>
<td>3.5 (2.6-4.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>7 (0.7)</td>
<td>177 (0.2)</td>
<td>4.0 (1.9-8.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Thyroid hormone abn.</td>
<td>9 (1.0)</td>
<td>395 (0.4)</td>
<td>2.3 (1.2-4.5)</td>
<td>0.014</td>
</tr>
<tr>
<td>Nutrition-related issues</td>
<td>10 (1.1)</td>
<td>762 (0.8)</td>
<td>1.3 (0.7-2.5)</td>
<td>0.390</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1 (0.1)</td>
<td>89 (0.1)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Congenital diseases</td>
<td>18 (1.9)</td>
<td>871 (0.9)</td>
<td>2.1 (1.3-3.4)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Concomitant hepatotoxic drug [ATC]</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotics [J01]</td>
<td>117 (12.5)</td>
<td>3398 (3.6)</td>
<td>3.5 (2.8-4.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anti-mycotics [J02]</td>
<td>1 (0.0)</td>
<td>41 (0.1)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Anti-tuberculosis [J04]</td>
<td>2 (0.2)</td>
<td>9 (0.1)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Anti-acids [A02]</td>
<td>8 (0.9)</td>
<td>141 (0.2)</td>
<td>5.8 (2.8-11.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anti-convulsants [N03]</td>
<td>12 (1.3)</td>
<td>323 (0.3)</td>
<td>3.7 (2.1-6.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anti-inflammatory [M01]</td>
<td>10 (1.1)</td>
<td>320 (0.3)</td>
<td>3.4 (1.8-6.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hormon preparations [G03]</td>
<td>10 (1.1)</td>
<td>678 (0.7)</td>
<td>1.8 (0.8-3.8)</td>
<td>0.133</td>
</tr>
<tr>
<td>Paracetamol [N02BE]</td>
<td>4 (0.4)</td>
<td>128 (0.1)</td>
<td>3.2 (1.2-8.7)</td>
<td>0.022</td>
</tr>
<tr>
<td>Psycoleptics [N05]</td>
<td>3 (0.3)</td>
<td>93 (0.1)</td>
<td>3.3 (1.0-10.4)</td>
<td>0.043</td>
</tr>
<tr>
<td>Psycoanaleptics [N06]</td>
<td>3 (0.3)</td>
<td>107 (0.1)</td>
<td>2.9 (0.9-9.1)</td>
<td>0.075</td>
</tr>
</tbody>
</table>
## Risk of Liver Injury with Antiasthma Medications

<table>
<thead>
<tr>
<th></th>
<th>Cases (N= 938)</th>
<th>Controls (N= 93665)</th>
<th>OR (CI 95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Use</td>
<td>572 (61%)</td>
<td>67539 (72%)</td>
<td>REF.</td>
</tr>
<tr>
<td>Current Use (&lt;30dys)</td>
<td>52 (6%)</td>
<td>2491 (3%)</td>
<td>2.51 (1.88-3.35)</td>
</tr>
<tr>
<td>Recent Use (30-180dys)</td>
<td>43 (5%)</td>
<td>2174 (2%)</td>
<td>2.12 (1.67-2.69)</td>
</tr>
<tr>
<td>Distant Use (180-365dys)</td>
<td>99 (11%)</td>
<td>6749 (7%)</td>
<td>1.73 (1.32-2.28)</td>
</tr>
<tr>
<td>Past Use (≥ 365dys)</td>
<td>172 (18%)</td>
<td>14712 (16%)</td>
<td>1.41 (1.18-1.68)</td>
</tr>
</tbody>
</table>

No further analyses within age group because of low exposure
RISK OF LIVER INJURY AND DIFFERENT CLASSES OF ANTI-ASTHMA MEDICATIONS*

*No cases for anticholinergics, cromons, and systemic drugs (B2-adreniergics, CS, Xanthines, and comb)
RISK OF LIVER INJURY AND SPECIFIC ANTI-ASTHMA MEDICATIONS*

*whole cohort*

- Montelukast (n=3)
- Budesonide (n=3)
- Beclometasone (n=18)
- Salbutamol (n=9)
- No use of any R03

*R03 users cohort*

- Montelukast (n=3)
- Budesonide (n=3)
- Beclometasone (n=18)
- Salbutamol (n=9)
- Past use of other R03

*with at least 3 exposed cases of liver toxicity*
LIMITATIONS

Misclassification
- outcome: unlikely, as manually validated cases
- exposure: adherence to the therapy (?)
  → possible risk underestimation

Confounding by indication
- restricted analysis within R03 users to control for it;

Residual confounding
- due to unmeasured severity of disease can never be excluded
CONCLUSIONS

- Liver injury seems to be associated with the use of some classes of anti-asthma medications in children and adolescents beyond the effect of the indication of use.

- Results need to be interpreted with caution:
  - β₂-agonists, ICS and LTRA showed a trend of association with hepatotoxicity but the effect of long/short treatment requires further investigation.
  - Larger exposure set is needed to estimate these potential associations as well as the effect of duration of treatment and of risk factors.