Mortality and cancer in paediatric inflammatory bowel disease: A population-based study


and the EPIMAD Group
Background

- In adult patients with IBD:
  - An inconsistent increased risk of mortality has been shown\(^1\)-\(^3\)
  - There is an increased risk of colonic and extra-intestinal cancers \(^4\)-\(^6\)

- In paediatric onset patients with IBD the risks of mortality and cancers remain poorly characterized

- Incidence of paediatric IBD continues to increase worldwide \(^7\)

- There is an increasing use of immunosuppressors and biologics in IBD paediatric patients \(^8\)

\(^1\) Romberg-Camps et al. Inflamm Bowel Dis 2010
\(^2\) Jess et al. Gut 2006
\(^3\) Duricova et al. Inflamm Bowel Dis 2010
\(^5\) Pedersen et al. Am J Gastroenterol 2010
\(^6\) Jess et al. Am J Gastroenterol 2010
\(^7\) Chouraki V et al. Aliment Pharmacol Ther 2011
\(^8\) Vernier-Massouille et al. Gastroenterology 2008
AIMS of the study

• The primary objective was to estimate the risks of mortality and cancers in a paediatric onset population-based IBD cohort.

• The secondary objective was to assess in cancer risk the role of immunosuppressors (IS) and biologics.
Patients & Methods (1)

- The EPIMAD Registry
- French population-based study \( (9.3\% \text{ of the whole French population}) \)
- Records all new incident IBD cases since 1988 \(^1\)

9,114 IBD patients recorded (1988-2004)

724 (7.9\%) paediatric onset IBD (<17 yrs)

Pediatric IBD diagnosis

- 538 (74\%) Indeterminate colitis
- 160 (22\%) Ulcerative colitis
- 26 (4\%) Crohn's disease

698 patients followed until 31/12/2009

\(^1\) Gower-Rousseau et al. Gut 1994
## Patients

<table>
<thead>
<tr>
<th></th>
<th>CD (n=538)</th>
<th>UC (n=160)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age at diagnosis [Q1-Q3]</strong></td>
<td><strong>14.6 [12.2-16.1]</strong></td>
<td><strong>14.5 [11.5-16.1]</strong></td>
</tr>
<tr>
<td><strong>Gender (male / female)</strong></td>
<td>293 / 245</td>
<td>67 / 93</td>
</tr>
<tr>
<td><strong>Median follow-up [Q1-Q3]</strong></td>
<td><strong>11.2 [7.4-15.1]</strong></td>
<td><strong>11.6 [8.2-15.8]</strong></td>
</tr>
<tr>
<td><strong>Location at diagnosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L1</td>
<td>14%</td>
<td>E1: 14%</td>
</tr>
<tr>
<td>L2</td>
<td>16%</td>
<td>E2: 26%</td>
</tr>
<tr>
<td>L3</td>
<td>70%</td>
<td>E3: 60%</td>
</tr>
<tr>
<td>L4</td>
<td>37%</td>
<td>-</td>
</tr>
<tr>
<td>APL</td>
<td>8.6%</td>
<td>-</td>
</tr>
<tr>
<td><strong>Behaviour at diagnosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B1</td>
<td>73%</td>
<td>-</td>
</tr>
<tr>
<td>B2</td>
<td>23%</td>
<td>-</td>
</tr>
<tr>
<td>B3</td>
<td>4%</td>
<td>-</td>
</tr>
<tr>
<td><strong>EIMs at diagnosis</strong></td>
<td>22%</td>
<td>20%</td>
</tr>
</tbody>
</table>

*according to Montreal classification*
Patients

<table>
<thead>
<tr>
<th></th>
<th>CD (n=538)</th>
<th>UC (n=160)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 ASA (in the 1st month after diagnosis)</td>
<td>93%</td>
<td>95%</td>
</tr>
<tr>
<td>Steroids (in the 1st month after diagnosis)</td>
<td>36%</td>
<td>27%</td>
</tr>
<tr>
<td>Cumulative probability of surgery (at 5yrs)</td>
<td>0.30</td>
<td>0.17</td>
</tr>
</tbody>
</table>

**Cumulative probability of treatment with immunosuppressors**
- **CD**: 69% (at 12 yrs)
- **UC**: 36% (at 12 yrs)

**Cumulative probability of treatment with an anti-TNFalpha**
- **CD**: 36% (at 12 yrs)
- **UC**: 6% (at 12 yrs)
Patients & Methods (4)

- Quantitative variables were expressed as median and interquartile range
- Only death and cancers occurring during follow-up were taken into account
- Calculation of expected cases were gender and age adjusted
  - According to the regional death rate (INSEE)
  - According to the FRANCIM cancer network
- Results were expressed as Standardized Ratio (SMR and SIR and 95% CI calculated by the exact Poisson method of Owen)
- The role of treatments in promoting cancer was evaluated using Standardized Incidence Ratio (SIR)
- Cumulative probabilities were estimated using Kaplan Meier curves
Results (1)

- 6 deaths were observed \((3 \text{ males}, 3 \text{ females})\)
- Crude mortality rate : 0.84%
- SMR : 1.3 [0.5 – 2.9] (NS)
- Median age at IBD diagnosis : 12 [7 – 17] years
- Median IBD duration at death : 13 [7 – 16] years
- Median age at death : 25 [19 – 30] years
Results (2)

6 deaths were observed

PSC: Primary Sclerosing Cholangitis
IS: Immunosuppressors
DS: Definitive Stoma

PSC
MOF/DS
Right colonic cancer
Nieman Pick Disease C
Nieman Pick Disease C
Road accident

UC
CD
CD

IBD 1991
IBD 1989
IBD 1993
IBD 1994
IBD 1990
IBD 1998

Colonic cancer

0 5 10 15 20 25 30 35 Years old
Results (3)

- 9 cancers were observed *(5 males, 4 females)*
- Crude cancer rate: 1.3 %

<table>
<thead>
<tr>
<th></th>
<th>Median (years)</th>
<th>Interquartile range</th>
</tr>
</thead>
<tbody>
<tr>
<td>age at IBD diagnosis</td>
<td>15</td>
<td>[10 – 17]</td>
</tr>
<tr>
<td>Time between IBD and cancer diagnosis</td>
<td>15</td>
<td>[10 – 17]</td>
</tr>
<tr>
<td>age at maximal follow-up</td>
<td>29</td>
<td>[27 – 36]</td>
</tr>
</tbody>
</table>
Results (4)

Global cancer Standardized Incidence Ratio
(age and gender adjusted)

SIR* : 3.0 [1.3 – 5.9]  p=0.012

* Excluding the case of in-situ uterine cervix cancer
Results (5)

- Left colonic and rectal cancers
- Right colonic cancer
- Cholangiocarcinoma
- Small bowel carcinoid tumor
- Basal cell carcinoma (abdomen)
- Basal cell carcinoma (face)
- In-situ uterine cervix cancer
- Epithelial penile cancer
- Acute lymphoblastic leukemia

Age:
- IBD 1989
- IBD 1990
- IBD 1992
- IBD 1993
- IBD 1996
- IBD 2001
- PSC

Conditions:
- UC
- CD
- Anti TNF
- IS
- DEATH
- Cancer

Cancers:
- PSC
- Cancer
- DEATH
## Results (6)

### SIR of cancer in paediatric onset IBD

(Univariate analysis)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Expected number</th>
<th>SIR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBD* (n=8)</td>
<td>2.70</td>
<td>3.0</td>
<td>[1.3 – 5.9]</td>
<td>0.012</td>
</tr>
<tr>
<td>UC (n=3)</td>
<td>0.65</td>
<td>4.6</td>
<td>[0.9 – 13.5]</td>
<td>0.06</td>
</tr>
<tr>
<td>CD* (n=5)</td>
<td>2.03</td>
<td>2.5</td>
<td>[0.8 – 5.8]</td>
<td>0.11</td>
</tr>
</tbody>
</table>

#### Cancer location

<table>
<thead>
<tr>
<th>Condition</th>
<th>Expected number</th>
<th>SIR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colonic cancer (n=2)</td>
<td>0.05</td>
<td>45.7</td>
<td>[5.5 – 165.3]</td>
<td>0.002</td>
</tr>
<tr>
<td>Basal cell carcinoma (n=2)</td>
<td>0.32</td>
<td>6.2</td>
<td>[0.8 – 22.3]</td>
<td>0.08</td>
</tr>
</tbody>
</table>

#### Treatment*

<table>
<thead>
<tr>
<th>Condition</th>
<th>Expected number</th>
<th>SIR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunosuppressors (IS) (n=4)</td>
<td>1.14</td>
<td>4.4</td>
<td>[1.4 – 10.1]</td>
<td>0.013</td>
</tr>
<tr>
<td>IS + Anti TNF (n=3)</td>
<td>0.38</td>
<td>8.0</td>
<td>[1.6 – 23.0]</td>
<td>0.013</td>
</tr>
</tbody>
</table>

* Excluding the case of in-situ uterine cervix cancer
Discussion

Strength

- Large paediatric onset IBD population based study (n=698)
- Large area covered (9.3% of the French population)
- Median follow-up is 11.5 years (range 3-22 years)
- References are Global French National Data

Weakness

- Small number of recorded events (6 deaths, 9 cancers)
- Multivariate analyses were not performed because of the small number of events
- Putative impact of treatments may be related to illness severity
Conclusions

- In this large paediatric onset population-based IBD cohort, mortality was not significantly different from that of the general population;

- We found:
  - a significant 3-fold increased risk of cancer with heterogeneous locations
  - mostly colonic cancer that is unfrequent in young patients of general population
  - no lymphoma or small bowel adenocarcinoma

- IS was associated with a 4-fold increased risk of cancer

- Association of IS with anti-TNF displayed a 8-fold increased risk of cancer*
  *The impact of anti TNF alone remains questionable as all anti TNF treated patients received IS too

- The presence of colon, skin and genital cancers pleads for a systematic screening in early onset IBD
Acknowledgements

- All adult & paediatric gastroenterologists of the EPIMAD area
- The 8 interviewer practitioners of the EPIMAD Registry
- Inserm (Institut National de la Santé et de la Recherche Médicale)
- InVS (Institut National Veille Sanitaire)
- Hôpitaux Universitaires de Lille, Amiens, Rouen
- Association François Aupetit
- Laboratoires Ferring
- Société Nationale Française de Gastroentérologie
- Laboratoires Astra-Zeneca