Oral curcumin is not more effective than placebo to prevent endoscopic postoperative recurrence in patients with Crohn's disease treated with concomitant thiopurines: the POPCUR trial


ECCO’ 19, Copenhaguen, Denmark
Disclosures

✓ Consulting fees:
  ✓ Abbvie, Amgen, Biogen, Janssen, Pfizer, Roche, Takeda

✓ Lecture fees:
  ✓ Abbvie, Amgen, Biogen, Ferring, Janssen, MSD, Pfizer, Roche, Takeda

✓ Grants:
  ✓ Abbvie, Pfizer, Takeda
Background

✓ Postoperative recurrence (POR) is a major concern in Crohn’s disease (CD)

A. Buisson et al. Aliment Pharmacol Ther 2012
Oral curcumin

- Anti-inflammatory and antioxidative properties
  - In cellular and rodent models
- Superior to placebo to induce endoscopic remission in ulcerative colitis

To evaluate whether oral curcumin therapy was more effective than placebo to prevent endoscopic POR in patients with CD treated with thiopurines
Methods

- **Randomized controlled trial**
  - 8 University Hospitals

- **Inclusion criteria:**
  - CD Patients with CD (> 18 years-old)
  - Undergoing ileocolonic resection
  - Macroscopic lesions had to be removed
  - Anastomosis had to be reached by colonoscopy

- **Exclusion criteria:**
  - Contra-indication to thiopurines
Design

Ileo-colonic resection*

RANDOMIZATION
Day 14 (± 7 days) following surgery

*Or closure of diverting stoma
Design

Ileo-colonic resection*

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Day 14 (± 7 days) following surgery

Azathioprine 2.0 -2.5 mg/kg/day
+ Oral curcumin 3g/day

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Ileo-colonic resection*

Randomization
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Azathioprine 2.0 - 2.5 mg/kg/day
+ Oral placebo

At 6 months

Central reading

Primary endpoint
- Endoscopic POR at M6
- Rutgeerts’ index ≥ 12

*Or closure of diverting stoma
Sample size calculation
- $\beta$-risk $\geq 80\%$
- Two-sided $\alpha$ level of .05
- To detect a relative difference of 50% with respect to the primary outcome
  - 50% in the placebo group vs 25% in the curcumin group
  - 5% of potential protocol deviations and withdrawal

$\Rightarrow$ Scheduled enrollment = 122 patients

Interim analysis planned after including 50% of patients
$\Rightarrow$ 62 patients

Intent-to-treat analyses
## Baseline characteristics

<table>
<thead>
<tr>
<th>n=62 patients</th>
<th>Placebo group</th>
<th>Curcumin group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=31</td>
<td>n=31*</td>
<td></td>
</tr>
<tr>
<td>Age at inclusion, (years), mean ± SD</td>
<td>37.6 ± 13.8</td>
<td>35.0 ± 10.5</td>
<td>0.39</td>
</tr>
<tr>
<td>Disease duration, (years), mean ± SD</td>
<td>8.3 ± 9.7</td>
<td>7.9 ± 6.7</td>
<td>0.64</td>
</tr>
<tr>
<td>Female gender, n (%)</td>
<td>25 (80.6%)</td>
<td>16 (53.3%)</td>
<td>0.031</td>
</tr>
<tr>
<td>Active smokers, n (%)</td>
<td>13 (41.9%)</td>
<td>7 (23.3%)</td>
<td>0.30</td>
</tr>
<tr>
<td>Prior bowel resection, n (%)</td>
<td>14 (45.1%)</td>
<td>14 (46.7%)</td>
<td>1.00</td>
</tr>
<tr>
<td>CD location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L1, n (%)</td>
<td>16 (51.6%)</td>
<td>11 (36.7%)</td>
<td>0.25</td>
</tr>
<tr>
<td>L2, n (%)</td>
<td>1 (3.2%)</td>
<td>0 (0.0%)</td>
<td>-</td>
</tr>
<tr>
<td>L3, n (%)</td>
<td>14 (45.2%)</td>
<td>19 (63.3%)</td>
<td>-</td>
</tr>
<tr>
<td>CD behaviour</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B1, n (%)</td>
<td>4 (12.9%)</td>
<td>7 (23.3%)</td>
<td>0.56</td>
</tr>
<tr>
<td>B2, n (%)</td>
<td>16 (51.6%)</td>
<td>12 (40.0%)</td>
<td>-</td>
</tr>
<tr>
<td>B3, n (%)</td>
<td>21 (35.5%)</td>
<td>11 (36.7%)</td>
<td>-</td>
</tr>
<tr>
<td>Perianal lesions, n (%)</td>
<td>5 (16.1%)</td>
<td>0 (0.0%)</td>
<td>0.053</td>
</tr>
<tr>
<td>Mean length of ileal resection, (cm), mean ± SD</td>
<td>22.7 ± 18.8</td>
<td>22.3 ± 13.7</td>
<td>0.92</td>
</tr>
<tr>
<td>Mean length of colonic resection (cm), mean ± SD</td>
<td>7.8 ± 10.4</td>
<td>5.0 ± 3.6</td>
<td>0.18</td>
</tr>
<tr>
<td>Immunosuppressants-naïve patients</td>
<td>12 (38.7%)</td>
<td>11 (36.7%)</td>
<td>0.84</td>
</tr>
<tr>
<td>Anti-TNF-naïve patients</td>
<td>4 (12.9%)</td>
<td>7 (23.3%)</td>
<td>0.34</td>
</tr>
</tbody>
</table>
Endoscopic POR* at 6 months

Rate of endoscopic postoperative recurrence at 6 months

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rate</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azathioprine + placebo (n=31)</td>
<td>58.1%</td>
<td>0.60</td>
</tr>
<tr>
<td>Azathioprine + curcumin (n=31)</td>
<td>67.7%</td>
<td></td>
</tr>
</tbody>
</table>

* Rutgeerts’ index ≥ i2
Endoscopic POR at 6 months

\[ p = 0.20 \]

Endoscopic postoperative recurrence ≥ i2b

- Azathioprine + placebo (n=31)
- Azathioprine + curcumin (n=31)
Endoscopic POR at 6 months

\[ p = 0.20 \]

\[ p = 0.034 \]

- **Endoscopic postoperative recurrence ≥ i2b**
  - Azathioprine + placebo (n=31): 41.9%
  - Azathioprine + curcumin (n=31): 54.8%

- **Endoscopic postoperative recurrence ≥ i3**
  - Azathioprine + placebo (n=31): 25.8%
Clinical POR at 6 months

<table>
<thead>
<tr>
<th>Clinical POR (CDAI &gt; 150), n (%)</th>
<th>Placebo group</th>
<th>Curcumin group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 (45.2%)</td>
<td>12 (38.7%)</td>
<td>0.80</td>
<td></td>
</tr>
<tr>
<td>Clinical POR (CDAI &gt; 200), n (%)</td>
<td>12 (38.7%)</td>
<td>9 (29.0%)</td>
<td>0.59</td>
</tr>
</tbody>
</table>
Quality of life at 6 months

<table>
<thead>
<tr>
<th>Quality of life (IBDQ*), mean ± SD</th>
<th>Placebo group</th>
<th>Curcumin group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>181.5 ± 24.7</td>
<td>178.5 ± 25.8</td>
<td>0.80</td>
<td></td>
</tr>
</tbody>
</table>

*Assessed using the IBD questionnaire*
Safety

\[ p = 0.42 \]

<table>
<thead>
<tr>
<th></th>
<th>Azathioprine + Placebo</th>
<th>Azathioprine + Curcumin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage</td>
<td>6.5%</td>
<td>12.9%</td>
</tr>
</tbody>
</table>
Severe adverse events

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo group</th>
<th>Curcumin group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migraine</td>
<td>-</td>
<td>1 (3.2 %)</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>1 (3.2 %)</td>
<td>-</td>
</tr>
<tr>
<td>Abdominal wall abscess</td>
<td>1 (3.2 %)</td>
<td>-</td>
</tr>
<tr>
<td>Nausea</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Carcinoma of the uterine cervix</td>
<td>-</td>
<td>1 (3.2 %)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>-</td>
<td>2 (6.4 %)</td>
</tr>
</tbody>
</table>

4 patients discontinued thiopurines due to adverse events (2 in each group)
Conclusions

✓ Oral curcumin was not more effective than placebo to prevent endoscopic POR in patients with CD receiving concomitant thiopurines

✓ Oral curcumin did not increase the risk of severe adverse events

✓ The POPCUR trial was discontinued after interim analysis

✓ We cannot recommend the use of oral curcumin in patients with CD
Aknowledgements

- **POPCUR study group**
  - **Clermont-Ferrand**: Gilles BOMMELAER, Marion GOUTTE, Dilek COBAN, Marie DODEL, Félix GOUTORBE, Christophe ALLIMANT, Maud REYMOND, Michel DAPOIGNY, Olivier ROUQUETTE, Emilie VAZIELLE
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