Anti-MAP therapy in Crohn’s disease: saviour or non-event?

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AUSTRALIA
Infectious agents in Crohn’s disease

- Pseudomonas (L forms)
- Chlamydia
- M. Kansasii
- Corynebacteria
- Viruses (= foreign bodies)
- Measles virus
- Listeria monocytogenes
- M. paratuberculosis
Mycobacterium paratuberculosis

- causes Johne’s disease
- atypical mycobacterium - MAC ss ptb
- rough cell wall
- obligate parasite of mammals
- facultative intracellular pathogen
- mycobactin dependent
- survives > 1 year in water/manure
**M. paratuberculosis and Crohn’s disease**

- Crohn’s disease similar to Johne’s disease
- “M Linda” isolated in 1984 - 3 of 11 patients
  - transmission to infant goats
  - confirmed as M paratuberculosis
- found in pasteurised milk
- spheroblast in culture
M. paratuberculosis and Crohn’s disease

- detected by PCR + culture in Crohn’s disease
  - tissue
  - blood
  - breast milk

- detection results highly variable
# M. paratuberculosis and Crohn’s disease

## Epidemiology

<table>
<thead>
<tr>
<th>PRO</th>
<th>CON</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clustering</td>
<td>No clustering</td>
</tr>
<tr>
<td>Similarities</td>
<td>Differences</td>
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</table>

## Clinical features

<table>
<thead>
<tr>
<th>PRO</th>
<th>CON</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-15%</td>
<td>0% or controls +ve</td>
</tr>
<tr>
<td>50%</td>
<td>22% in UC</td>
</tr>
</tbody>
</table>

## Isolation - tissue

<table>
<thead>
<tr>
<th>PRO</th>
<th>CON</th>
</tr>
</thead>
<tbody>
<tr>
<td>65-100%</td>
<td>0%; 0-100% in controls</td>
</tr>
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</table>

## Isolation - blood

<table>
<thead>
<tr>
<th>PRO</th>
<th>CON</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ve</td>
<td>-ve or +ve controls</td>
</tr>
</tbody>
</table>

## PCR for DNA

<table>
<thead>
<tr>
<th>PRO</th>
<th>CON</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anecdotal</td>
<td>Small controlled trial (C+R)</td>
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</table>

## Antibodies

<table>
<thead>
<tr>
<th>PRO</th>
<th>CON</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
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</table>

## EM

<table>
<thead>
<tr>
<th>PRO</th>
<th>CON</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No visible organism</td>
</tr>
</tbody>
</table>

Commensal or pathogen?
Antibiotics for M paratuberculosis

CONSIDERATIONS

- intracellular
- spheroplast
- slow growth
- long duration of therapy
- drug resistance
- little animal data
Antimycobacterial antibiotics in Crohn’s disease

- Isoniazid
- Rifampycin
- Pyrazinamide
- Dapsone
- Clarithromycin*
- Rifabutin*
- Clofazimine*
- Ethambutol*
- Azithromycin*

* Activity against M PTB

Conventional antituberculous regimens ineffective
Anti-paratuberculosis therapy in Crohn’s disease

Gui et al, 1997

52 patients

46.5% post-op

6 intolerant

46

rifabutin + clarithromycin

43

rifabutin + azithromycin

3

Duration of therapy: 18.7 m (6-35m)

Duration of follow-up: 25.1 m (7-41m)
Anti-paratuberculosis therapy in Crohn’s disease

Gui et al, 1997 (cont)

Harvey-Bradshaw index

Time after starting antibiotic therapy

N=46
N=46
N=40
N=35
N=23

p=0.004
p<0.001
p=0.003
p<0.001
Anti-paratuberculosis therapy in Crohn’s disease

Gui et al, 1997 (cont)

Proportion of patients in remission (%)

32.6% required surgery
Australian APT trial in Crohn’s disease

Aim: to determine whether 2 years of anti-paratuberculosis therapy (APT) in patients with Crohn’s disease has a prolonged benefit seen after the treatment is completed.
Combination anti-paratuberculosis therapy (APT) with clarithromycin, rifabutin and clofazimine for the treatment of Crohn’s Disease

W Selby, B Crotty, T Florin, P Pavli and the APT study group

- An Australia-wide multicentre trial
- 2 years of antibiotics or placebo in addition to other therapy
- 1 year follow-up after treatment
- Investigator-initiated; sponsored by Pharmacia/Pfizer
**APT trial in Crohn’s disease**

- **Antibiotics**
  - **Clarithromycin** 750mg/day
  - **Rifabutin** 450mg/day
  - **Clofazimine** 50mg/day

  Failure of dissolution of outer gelatin shell in vitro from August 2001 - June 2002
**APT trial in Crohn’s disease**

**Study design**

**Week 0**
- APT or Placebo + prednisolone 40mg/day

**Week 16**
- REMISSION
- NO REMISSION 
- WITHERDRAWN

### Flowchart:

- **APT or Placebo**
  - **2 years**
    - **REMISSION**
      - Prednisolone ± Withdraw
        - **1 year**
          - **TERMINATION**
**APT trial in Crohn’s disease**

- **Primary outcomes**
  - relapse at 1 and 2 years
  - relapse at 3 years (1 year after treatment)

- **Secondary outcomes**
  - remission at 16 weeks (CDAI ≤ 150)
  - safety
  - endoscopic findings
  - quality of life
**APT trial in Crohn’s disease**

**Inclusion criteria**
- age $\geq$ 18 years
- CDAI $\geq$ 200
- able to tolerate corticosteroids
- no antibiotic therapy for Crohn’s disease

**Exclusion criteria**
- prednisone $> 10$mg/day
- recent immunomodulator therapy (≤ 6 months)
- ileostomy
APT trial in Crohn’s disease

- 213 Subjects enrolled (212 required)
  - 101 males 112 females
  - mean age 35.6 ± 10.7 years (18-70yrs)
  - recruited Sept 1999 to Sept 2001
  - stratified for azathioprine/6-MP
### APT trial in Crohn’s disease

#### Subject groups

<table>
<thead>
<tr>
<th></th>
<th>APT</th>
<th>Placebo</th>
</tr>
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<tbody>
<tr>
<td>No.</td>
<td>102</td>
<td>111</td>
</tr>
<tr>
<td>M:F</td>
<td>51:51</td>
<td>50:61</td>
</tr>
<tr>
<td>Age</td>
<td>36.5 ± 11.3</td>
<td>34.8 ± 10.0</td>
</tr>
<tr>
<td>Smokers</td>
<td>33%</td>
<td>43%</td>
</tr>
<tr>
<td>Duration of disease</td>
<td>8.1 ± 7.2 yrs</td>
<td>8.7 ± 7.3 yrs</td>
</tr>
<tr>
<td>Site of disease – ileum</td>
<td>30</td>
<td>34</td>
</tr>
<tr>
<td>colonic</td>
<td>41</td>
<td>36</td>
</tr>
<tr>
<td>ileocolonic</td>
<td>31</td>
<td>38*</td>
</tr>
<tr>
<td>Azathioprine/6-MP</td>
<td>35</td>
<td>32</td>
</tr>
<tr>
<td>CDAI</td>
<td>291 ± 72.5</td>
<td>282 ± 75.0</td>
</tr>
</tbody>
</table>
# APT trial in Crohn’s disease

## Patient disposition

<table>
<thead>
<tr>
<th>ENTRY</th>
<th>APT</th>
<th>PLACEBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>102</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>213</td>
<td>111</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+ prednisolone 40mg/day</td>
</tr>
</tbody>
</table>

- **Week 16:** 122 for primary analysis
- **Week 52:**
  - APT: 45
  - PLACEBO: 29
  - APT or Placebo
- **Week 104:**
  - APT: 34
  - PLACEBO: 20
  - Follow-up
- **Week 156:**
  - APT: 19
  - PLACEBO: 13
  - Follow-up

- **Week 156**
  - 91 withdrawn

The table represents the number of patients in each group at different time points, with the APT group starting with 102 patients and the PLACEBO group with 111 patients. The difference in withdrawals is highlighted, showing 91 patients withdrew from the APT group. The final follow-up indicates the number of patients remaining in each group.
**APT trial in Crohn’s disease**

**Relapse rates**

- 52 weeks (1 year treatment)

- APT Placebo
  - 39% (26/67)
  - $\bar{p} = 0.054$
  - APT vs Placebo
    - OR 2.04 (0.84-4.93)
    - NOT SIGNIFICANT ($p<0.017$ needed)

- Placebo
  - 56% (31/55)
APT trial in Crohn’s disease

Relapse rates

104 weeks (2 years treatment)

- APT
  - 26% (11/42)

- Placebo
  - 43% (12/28)

\[ OR_{APT \text{ vs Placebo}} = 2.22 \ (0.62-7.96) \]

- p = 0.14
- NOT SIGNIFICANT
APT trial in Crohn’s disease

Relapse rates

156 weeks (1 year follow up)

APT Placebo

59% (20/34) 50% (10/20)

p = 0.54

OR APT vs Placebo 0.70 (0.18-2.74)

NOT SIGNIFICANT

APT Placebo

Remission 14 10
**APT trial in Crohn’s disease**

**Primary analysis**

- No. of subjects in remission
  - 67 APT
  - 55 placebo

- Treatment period:
  - 16 weeks
  - 12 months
  - 24 months
  - 36 months

- P=0.02

- NS
APT trial in Crohn’s disease

- No influence of:
  - age
  - disease site
  - previous surgery for Crohn’s disease
  - smoking status
  - oral contraceptive

- Azathioprine/6-MP
  - positive benefit weeks 17-52
  - negative benefit weeks 53-104
**APT trial in Crohn’s disease**

**Remission at 16 weeks**
- APT: 102 (66%)
- Placebo: 111 (51%)

Secondary variable

- OR APT vs Placebo: 0.51 (0.30-0.90)
- p = 0.02
**APT trial in Crohn’s disease**

- No differences in:
  - number or relapses
  - time to relapse
  - endoscopic score (CDEIS)
    - remission at 156 weeks
      - 9/23 APT
      - 4/15 Placebo
  - surgery (11)
    - 6 APT
    - 5 Placebo
**APT trial in Crohn’s disease**

**Adverse events**

- significant increase in APT group in:
  - abnormal LFTs (2.3% weeks 0-16)
  - vaginal candidiasis
  - urine discoloration
  - arthralgia
  - tooth discoloration

- withdrawals for AE
  - APT 9
  - Placebo 7
## APT trial in Crohn’s disease

### Assessment of Blinding

<table>
<thead>
<tr>
<th></th>
<th>Subject</th>
<th></th>
<th></th>
<th>Physician</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>APT</td>
<td>Placebo</td>
<td>Unknown</td>
<td>APT</td>
<td>Placebo</td>
<td>Unknown</td>
</tr>
<tr>
<td>Week 52</td>
<td>71%</td>
<td>7%</td>
<td>21%</td>
<td>73%</td>
<td>11%</td>
<td>16%</td>
</tr>
<tr>
<td>Week 104</td>
<td>73%</td>
<td>11%</td>
<td>16%</td>
<td>55%</td>
<td>26%</td>
<td>19%</td>
</tr>
<tr>
<td>Week 52</td>
<td>61%</td>
<td>5%</td>
<td>34%</td>
<td>32%</td>
<td>14%</td>
<td>54%</td>
</tr>
<tr>
<td>Week 104</td>
<td>61%</td>
<td>7%</td>
<td>32%</td>
<td>35%</td>
<td>20%</td>
<td>45%</td>
</tr>
</tbody>
</table>

Physician/patient concordance 52% at 1 year and 60% at 2 years
**APT trial in Crohn’s disease**

**Summary**

- APT treatment with clarithromycin, rifabutin and clofazimine has a short-term benefit in addition to corticosteroids up to 16 weeks.

- There is no carry-over effect up to 24 months of continued therapy, either clinically or endoscopically.

- Relapse continues to occur after APT is ceased.

- Adverse events were more common in the treatment group but were usually not severe.
APT trial in Crohn’s disease

Specific issues

1. Number of subjects
   - recruitment target met
   - selection for antibiotic responders
APT trial in Crohn’s disease

Specific issues

2. Number of antibiotics

3. Duration of therapy
Anti-paratuberculosis therapy in Crohn’s disease

Gui et al, 1997

- 46 patients – **clarithromycin + rifabutin** (43)/azithromycin (3)
- **18.7 months** treatment (6-35m)
- **25.1 months** follow-up (7-41m)
Anti-paratuberculosis therapy in Crohn’s disease

Open label studies

Leipar et al, 2000
- 25 patients
- Clarithromycin 500mg/d for 4-12 weeks
- 64% ≥ 3 point fall in Harvey-Bradshaw index
- 48% remission
- Remission maintained in 8 of 11 with continued treatment

Shafran et al, 2002
- 36 patients – 29 tolerated medications
- Clarithromycin 500mg/d + rifabutin 300mg/d for 4-17m
- 58% fall ≥ 70 in CDAI
- Remission rates not given
Anti-paratuberculosis therapy in Crohn’s disease

Open label studies

Borody et al, 2002

- 12 patients

- Clarithromycin 750mg/d + rifabutin 450mg/d + clofazimine 2mg/kg/d up to 54 months

- 6/12 “full response”
  - 3/6 in remission off treatment up to 26 months
**Clarithromycin + ethambutol in Crohn’s disease**

- 31 patients with increased permeability
- Clarithromycin 500mg bd + ethambutol 15mg/kg/day vs placebo
- 3 months treatment with follow-up to 12 months

**Graphical Representation:**

- Δ in Harvey-Bradshaw Index vs Months
- Antibiotics: Yellow
- Placebo: Blue
- Rx

**Legend:**

- Small numbers
- Less than half active disease

*Goodgame et al, 2001*
APT trial in Crohn’s disease

Specific issues

4. No testing for MAP
Studies **NOT REPORTING** MAP status

- Gui et al, 1997
- Leipar et al, 2000
- Shafran et al, 2002
- Borody et al, 2002
APT in Crohn’s disease

Studies REPORTING MAP status
Testing for MAP - possibilities

- if positive – no effect of APT
- if negative – MAP not playing a role in these subjects
- subset not excluded but would be small
Anti-paratuberculosis therapy in Crohn’s disease

Conclusions

- antibiotic therapy can induce remission in patients with Crohn’s disease, using a variety of combinations, including APT

- long term benefit is not seen with continued APT therapy after remission is achieved

- the results of the Australian APT trial do not provide evidence for a “cure” of Crohn’s disease with this treatment

- The findings also argue against a role of continuing M. paratuberculosis infection in the pathogenesis of Crohn’s disease
Anti-MAP therapy in Crohn’s disease: saviour or non-event?
**APT trial in Crohn’s disease**

**Acknowledgements:**

- Dr Brendan Crotty, Dr Paul Pavli, Dr Tim Florin
- The APT study group (W Selby, P Pavli, B Crotty, T Florin, G Radford-Smith, PR Gibson, B Mitchell, W Connell, R Read, M Merrett, D Hetzel, N Hoffmann, H Ee, M Pekin, N Talley, B Collins, P Bampton, H Jackson, P Stephenson, R Batey, P Katelaris and S Kolt)
- Pfizer (Pharmacia & Upjohn)
- The Australian Crohn’s and Colitis Association (ACCA)
Effect of azathioprine/6-MP

Relapse at 52 weeks

<table>
<thead>
<tr>
<th></th>
<th>APT</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>Aza/6-MP</td>
<td>24%</td>
<td>76%</td>
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<tr>
<td>No aza/6-MP</td>
<td>46%</td>
<td>47%</td>
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p =0.01 for azathioprine/6-MP
APT in Crohn’s disease

Effect of azathioprine/6-MP

Relapse at 104 weeks

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<th>Placebo</th>
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<tbody>
<tr>
<td>Aza/6-MP</td>
<td>38%</td>
<td>20%</td>
</tr>
<tr>
<td>No aza/6-MP</td>
<td>19%</td>
<td>48%</td>
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</table>

p = 0.04 for no azathioprine/6-MP