Old and new steroids: hitting the target

Silvio Danese, MD, PhD
IBD Center
Division of Gastroenterology
Istituto Clinico Humanitas, Milan, Italy
I Admit......
I still use steroids in 2012!

When everything started???
“Pilot plan factory” for extracting steroids from adrenal glands*

1930

*Processing capacity
800 pounds of beef per week
Steroids in IBD – Landmark Papers

1951

THE EFFECT OF CORTISONE ON THE CLINICAL COURSE OF CHRONIC REGIONAL ENTERITIS AND CHRONIC IDIOPATHIC ULCERATIVE COLITIS

By THOMAS E. MACHELLA, M.D., and (by invitation) O. ROGER HOLLAN, M.D.*

PHILA. PENNA.

1954-5

CORTISONE IN ULCERATIVE COLITIS
PRELIMINARY REPORT ON A THERAPEUTIC TRIAL

By S. C. TRUELOVE, M.D., M.R.C.P. AND L. J. WITTS, M.D., F.R.C.P.
Nuffield Department of Clinical Medicine, Radcliffe Infirmary, Oxford

1979

National Cooperative Crohn’s Disease Study: Results of Drug Treatment

1983

European Cooperative Crohn’s Disease Study (ECCDS): Results of Drug Treatment
Steroids are probably still one of the most effective drugs we have in our IBD therapeutic armamentarium.
What makes steroids angels or devils in IBD in 2012?
What makes steroids angels or devils in IBD in 2012?

- Very effective
- Inactive
- Disease

- Side effects

Efficacy vs. Safety
Early recognition of side-effects

Preliminary Communications

Oral Betamethasone 17-Valerate in Chronic Ulcerative Colitis and Crohn's Disease


During 10 years' experience in the use of corticosteroids as the mainstay of treatment of 50 patients suffering from ulcerative colitis we have found that a drug lacking the potentially disastrous side-effects of these agents has become increasingly necessary.

A. Morton Gill, M.D., F.R.C.P.
A. T. Otaki, M.B., M.R.C.P.
J. R. Daly, M.B., B.S.
J. Spencer-Peet, M.B., B.S.

From the Gastro-enterological Clinic and Department of Chemical Pathology, West London Hospital.
Steroids have serious side effects

- Osteoporosis/osteonecrosis
- Higher risk of infections
- Oedema/cushing syndrome
- Cataracts/glaucoma
- Growth retardation
- Behavioural changes
- Striae
- Diabetes
- Cardiovascular complications
Increased risk of infections and mortality associated with steroid use

**Multivariate analysis**

<table>
<thead>
<tr>
<th>Mortality</th>
<th>Serious infections</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Odds Ratio</strong></td>
<td><strong>Odds Ratio</strong></td>
</tr>
<tr>
<td>IFX</td>
<td>AZA 6-MP MTX</td>
</tr>
<tr>
<td>*p=0.001; †p&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

Lichtenstein GR, TREAT registry, Clin Gastroenterol Hepatol. 2006
Novel steroid formulations: 
Hitting the target?.....
....BUT....higher efficacy, less toxicity?
# Budesonide: A synthetic steroid with low systemic bioavailability

<table>
<thead>
<tr>
<th></th>
<th>Prednisolone</th>
<th>Budesonide</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Site</strong></td>
<td>Small bowel</td>
<td>Ileo-caecal</td>
</tr>
<tr>
<td><strong>Absorption</strong></td>
<td>95-100%</td>
<td>60-80%</td>
</tr>
<tr>
<td><strong>T max</strong></td>
<td>1-3 hours</td>
<td>4.3 hours</td>
</tr>
<tr>
<td><strong>T ½</strong></td>
<td>3 hours</td>
<td>4 hours</td>
</tr>
<tr>
<td><strong>F</strong></td>
<td>70-85%</td>
<td>11%</td>
</tr>
</tbody>
</table>

Currently available formulations: “Controlled ileal release” (Entocort®) and “pH dependent”

CYP 3A4

6β-hydroxybudesonide

16α-hydroxy-prednisolone

Budesonide is superior to placebo at inducing remission in CD

n = 258
- 119 (46%) withdrew
- 96 – therapeutic failure
- 13 – ADRs
- 10 – non-compliance
### Budesonida vs. Placebo: in inducing remission

<table>
<thead>
<tr>
<th>Estudio</th>
<th>Budesonida n/N</th>
<th>Placebo n/N</th>
<th>Coeficiente de disparidad (Fijo)</th>
<th>Ponderación (%)</th>
<th>Coeficiente de disparidad (Fijo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greenberg 1994</td>
<td>31 / 61</td>
<td>13 / 66</td>
<td></td>
<td>37.1</td>
<td>4.21 [1.92, 9.26]</td>
</tr>
<tr>
<td>Tremaine 2002</td>
<td>78 / 157</td>
<td>13 / 40</td>
<td></td>
<td>82.9</td>
<td>2.05 [0.99, 4.26]</td>
</tr>
<tr>
<td><strong>Total (95% IC)</strong></td>
<td><strong>109 / 218</strong></td>
<td><strong>28 / 106</strong></td>
<td></td>
<td><strong>100.0</strong></td>
<td><strong>2.85 [1.67, 4.87]</strong></td>
</tr>
</tbody>
</table>

Prueba de heterogeneidad chiquadrado = 1.72 gl = 1 p = 0.1893
Prueba de efecto general Z = 3.68 p = 0.0001

Favorece al placebo

![Graph showing the results of the comparison between Budesonida and Placebo in inducing remission.](image)
Budesonide vs Mesalazine (2 gr) for inducing remission in CD

CLINICAL—ALIMENTARY TRACT

Budesonide 9 mg Is at Least as Effective as Mesalamine 4.5 g in Patients With Mildly to Moderately Active Crohn’s Disease

ANDREAS TROMM,* IVAN BUNGANIČ,‡ EVA TOMSOVÁ,§ ZSOLT TULASSAY,¶ MILAN LUKÁŠ,* JAN KYKAL,* MARIAN BÁTOVKY,*** BOHUMIL FIXA,†† LIBOR GABALEC,§§ RIFAAT SAFADI,††† HEINZ-JOCHEM KRAMM,†††† ISTVÁN ALTORJAY,‡‡ HANNS LÖHR,*** IOANNIS KOUTROUBAKIS,††† SIMON BAR-MEIR,§§§ DAVOR ŠTIMAC,††† ELKE SCHÄFFLER,* CHRISTOPH GLASMACHER,†††† KARIN DILGER,‡‡‡ RALF MOHRBACHER,‡‡‡ ROLAND GREINWALD,*** and the International Budesonide Study Group

P=.001 non-inferiority 95% RCI -4.6%, 18.0%  
ITT  
69.5% 62.1% 
Budesonide (n=154) Mesalamine (n=153) 
P=.014 non-inferiority 95% RCI -8.7%, 15.5%  
PP  
72.4% 68.9% 
Budesonide (n=134) Mesalamine (n=119)
Budesonide is equivalent to prednisolone in inducing remission in CD

**Graph:**
- Patients in remission (%) over weeks of treatment (2, 4, 6, 8, 10) for Prednisolone and Budesonide.

**Table:**

<table>
<thead>
<tr>
<th>Weeks of Treatment</th>
<th>Pred (%)</th>
<th>Bud (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>56</td>
<td>45</td>
<td>0.22</td>
</tr>
<tr>
<td>4</td>
<td>67</td>
<td>40</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6</td>
<td>65</td>
<td>52</td>
<td>0.12</td>
</tr>
<tr>
<td>8</td>
<td>66</td>
<td>53</td>
<td>0.12</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

n = 176

- 31(18%) withdrew
  - 23 – therapeutic failure
  - 3 – ADRs
  - 2 – non-compliance
  - 1 - pregnancy
Cochrane Review: Efficacy of Budesonide vs Prednisolone in induction of remission

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Budesonide n/N</th>
<th>Conventional steroid n/N</th>
<th>Risk Ratio M-H,Random,95% CI</th>
<th>Risk Ratio M-H,Random,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>3–8 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bar-Meir 1998</td>
<td>51/100</td>
<td>56/101</td>
<td>0.92 [0.71, 1.19]</td>
<td></td>
</tr>
<tr>
<td>Campieri 1997</td>
<td>61/119</td>
<td>35/58</td>
<td>0.85 [0.65, 1.12]</td>
<td></td>
</tr>
<tr>
<td>Escher 2004</td>
<td>12/22</td>
<td>17/26</td>
<td>0.83 [0.52, 1.34]</td>
<td></td>
</tr>
<tr>
<td>Gross 1996</td>
<td>19/34</td>
<td>24/33</td>
<td>0.77 [0.53, 1.11]</td>
<td></td>
</tr>
<tr>
<td>Levine 2003</td>
<td>8/19</td>
<td>6/14</td>
<td>0.98 [0.44, 2.19]</td>
<td></td>
</tr>
<tr>
<td>Rutgeerts 1994</td>
<td>45/88</td>
<td>56/88</td>
<td>0.80 [0.62, 1.04]</td>
<td></td>
</tr>
<tr>
<td>Tursi 2006</td>
<td>10/15</td>
<td>8/15</td>
<td>1.25 [0.69, 2.26]</td>
<td></td>
</tr>
<tr>
<td>Van lensel 1995</td>
<td>5/9</td>
<td>8/8</td>
<td>0.63 [0.33, 1.17]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>406</strong></td>
<td><strong>344</strong></td>
<td><strong>0.85 [0.75, 0.97]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 271 (Budesonide), 210 (Conventional steroid)
Heterogeneity: Tau² = 0.0; Chi² = 3.52, df = 7 (P = 0.83); I² =0.0%
Test for overall effect: Z = 2.5 (P = 0.012)
Cochrane Review: Budesonide vs Prednisolone adverse events

Review: Budesonide for induction of remission in Crohn’s disease
Comparison: 2 Budesonide 9 mg vs. conventional steroids
Outcome: 7 Corticosteroid related adverse events

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Budesonide</th>
<th>Conventional steroid</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Random,95% CI</td>
<td></td>
<td>M-H,Random,95% CI</td>
</tr>
<tr>
<td>Bar-Meir 1998</td>
<td>44/100</td>
<td>68/101</td>
<td></td>
<td>30.5 %</td>
<td>0.65 [0.50, 0.85]</td>
</tr>
<tr>
<td>Campieri 1997</td>
<td>56/119</td>
<td>34/58</td>
<td></td>
<td>26.1 %</td>
<td>0.80 [0.60, 1.07]</td>
</tr>
<tr>
<td>Escher 2004</td>
<td>11/22</td>
<td>20/26</td>
<td></td>
<td>11.6 %</td>
<td>0.65 [0.41, 1.04]</td>
</tr>
<tr>
<td>Gross 1996</td>
<td>10/35</td>
<td>23/33</td>
<td></td>
<td>8.1 %</td>
<td>0.41 [0.23, 0.72]</td>
</tr>
<tr>
<td>Levine 2003</td>
<td>6/19</td>
<td>10/14</td>
<td></td>
<td>4.9 %</td>
<td>0.44 [0.21, 0.93]</td>
</tr>
<tr>
<td>Rutgeerts 1994</td>
<td>29/88</td>
<td>48/88</td>
<td></td>
<td>18.8 %</td>
<td>0.60 [0.42, 0.86]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>383</strong></td>
<td><strong>320</strong></td>
<td></td>
<td><strong>100.0 %</strong></td>
<td><strong>0.64 [0.54, 0.76]</strong></td>
</tr>
</tbody>
</table>

Total events: 156 (Budesonide), 203 (Conventional steroid)
Heterogeneity: Tau² = 0.01; Chi² = 5.85, df = 5 (P = 0.32); I² = 15%
Test for overall effect: Z = 5.14 (P < 0.000001)
## Budesonide in remission maintenance

<table>
<thead>
<tr>
<th>Study</th>
<th>Favours Treatment</th>
<th>Favours Control</th>
<th>Relative Risk (Fixed)</th>
<th>Weight (%)</th>
<th>Relative Risk (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>95% CI</td>
<td></td>
<td>95% CI</td>
</tr>
<tr>
<td><strong>01 Budesonide 6 mg/day vs placebo</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferguson 1998</td>
<td>11/22</td>
<td>17/27</td>
<td>26.5</td>
<td>0.79</td>
<td>[0.48, 1.32]</td>
</tr>
<tr>
<td>Greenberg 1996</td>
<td>22/36</td>
<td>24/36</td>
<td>41.6</td>
<td>0.92</td>
<td>[0.65, 1.30]</td>
</tr>
<tr>
<td>Lofberg 1996</td>
<td>19/32</td>
<td>17/27</td>
<td>32.0</td>
<td>0.94</td>
<td>[0.63, 1.42]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>90</strong></td>
<td><strong>90</strong></td>
<td><strong>100.0</strong></td>
<td><strong>0.89</strong></td>
<td><strong>0.71, 1.13</strong></td>
</tr>
</tbody>
</table>

Total events: 52 (Favours Treatment), 58 (Favours Control)
Test for heterogeneity chi-square=0.30 df=2 p=0.86 P =0.0%
Test for overall effect z=0.94 p=0.3

| **02 Budesonide 6 mg/day vs budesonide 3 mg/day** |                           |                           |                       |            |                       |
| spinach       | 11/22             | 12/26             | 18.8                  | 1.08       | [0.60, 1.95]          |
| Greenberg 1996| 22/36             | 23/33             | 41.1                  | 0.88       | [0.62, 1.24]          |
| Lofberg 1996  | 19/32             | 23/31             | 40.0                  | 0.80       | [0.56, 1.14]          |
| **Subtotal (95% CI)** | **90**           | **90**          | **100.0**             | **0.89**   | **0.70, 1.11**        |

Total events: 52 (Favours Treatment), 58 (Favours Control)
Test for heterogeneity chi-square=0.77 df=2 p=0.68 P =0.0%
Test for overall effect z=1.04 p=0.3

| **03 Budesonide 3 mg/day vs placebo** |                           |                           |                       |            |                       |
| spinach       | 12/26             | 17/27             | 28.9                  | 0.73       | [0.44, 1.22]          |
| Greenberg 1996| 23/33             | 24/36             | 39.7                  | 1.05       | [0.76, 1.44]          |
| Lofberg 1996  | 23/31             | 17/27             | 31.4                  | 1.18       | [0.83, 1.68]          |
| **Subtotal (95% CI)** | **90**           | **90**          | **100.0**             | **1.00**   | **0.80, 1.24**        |

Total events: 58 (Favours Treatment), 58 (Favours Control)
Test for heterogeneity chi-square=2.35 df=2 p=0.31 P =14.8%
Test for overall effect z=0.03 p=1

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Simms L & Steinhart AH. The Cochrane Library 2007
Hitting the target…BUT…
Higher efficacy, less toxicity?

SUMMARY BUDESONIDE

- Head to head with systemic steroids Available
- Almost Equal efficacy
- Better safety profile for budesonide
NEW STEROID FORMULATIONS

- (Italians like investigating NEW STEROID FORMULATIONS)

World cup 2006: Italy against France
1. Italian solutions to steroid adverse events!

New delivery systems
How to hit the target (entire colon) in UC with budesonide?

Oral dosage forms

Site of action of existing treatments

Enemas, suppositories and foams
The Multi Matrix System (MMX™)

- Gastroprotectant layer
- LV hydrophilic - amphipatic polymer matrix
- HV hydrophilic polym. matrix
- Inert matrix material
- Drug (+ excipient)

Hydrophilic matrix

Inert matrix
Entire colon is targeted (pharmaco-scintigraphy)

1h 30m duodenum

4h 30m ascending colon

7h 30m transverse colon

10h transverse colon

16h descending colon

24h rectum
Budesonide MMX®
Comparative Pharmacokinetics

- Bioavailability profile of budesonide MMX® (6 and 9 mg tablets) compared to a controlled ileal-release formulation, Entocort® EC 9 mg (3 x 3 mg) capsules in healthy volunteers

![Graph showing concentration over time for Budesonide MMX 6 mg, Budesonide MMX 9 mg, and Entocort® EC 3 mg x 3 capsules.](image-url)
Budesonide-MMX® 9mg

Completed phase III trials in active mild to moderate UC

- MMX 9mg vs 6mg vs Entocort® vs placebo (EU)
- MMX 9mg vs 6mg vs Asacol® 2.4g vs placebo (US)

<table>
<thead>
<tr>
<th>Primary Endpoint</th>
<th>Remission at week 8, defined as:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• UCDAI score ≤ 1 with:</td>
</tr>
<tr>
<td></td>
<td>• Rectal bleeding and stool frequency score = 0 AND</td>
</tr>
<tr>
<td></td>
<td>• Normal mucosa (no friability) on endoscopy AND</td>
</tr>
<tr>
<td></td>
<td>• Endoscopic Index Score with ≥ 1 point reduction from baseline</td>
</tr>
</tbody>
</table>

UCDAI score components: stool frequency, rectal bleeding, mucosal appearance and physician rating of disease activity
Budesonide MMX® phase 3 study results (EU) primary efficacy endpoint

Remission rates after 8 weeks of treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Remission, n (%)</th>
<th>Δ vs. Placebo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>89</td>
<td>4 (4.5)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>MMX 9 mg</td>
<td>109</td>
<td>19 (17.4)</td>
<td>12.9%</td>
<td>0.0047*</td>
</tr>
<tr>
<td>MMX 6 mg</td>
<td>109</td>
<td>9 (8.3)</td>
<td>3.8%</td>
<td>0.2876</td>
</tr>
<tr>
<td>Entocort EC</td>
<td>103</td>
<td>13 (12.6)</td>
<td>8.1%</td>
<td>0.0481</td>
</tr>
</tbody>
</table>

* Statistically significant (p < 0.025)
+ Statistically significant (p < 0.05)
Study not powered to show a statistical difference between budesonide MMX and Entocort treatment arms

Travis et al, DDW 2011
Remission at week 8 (USA)
primary efficacy endpoint

N = 489 (modified ITT Population)

**Remission, n (%)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N = 121</th>
<th>N = 123</th>
<th>N = 121</th>
<th>N = 124</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission, n (%)</td>
<td>9 (7.4)</td>
<td>22 (17.9)</td>
<td>16 (13.2)</td>
<td>15 (12.1)</td>
</tr>
<tr>
<td>Δ vs. Placebo</td>
<td>--</td>
<td>10.4%</td>
<td>5.8%</td>
<td>4.7%</td>
</tr>
<tr>
<td>P-value</td>
<td>--</td>
<td><strong>0.0143</strong>*</td>
<td>0.1393</td>
<td>0.2200</td>
</tr>
</tbody>
</table>

* Statistically significant (p < 0.025)
Not powered to show statistical difference between Budesonide MMX treatment arms and Asacol
<table>
<thead>
<tr>
<th>Effect</th>
<th>Placebo N=129</th>
<th>MMX 9 mg N=128</th>
<th>MMX 6 mg N=128</th>
<th>Entocort 9 mg N=126</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>Overall</td>
<td>10 (7.9)</td>
<td>7 (5.5)</td>
<td>6 (4.7)</td>
<td>10 (7.9)</td>
</tr>
<tr>
<td>Moon Face</td>
<td>4 (3.1)</td>
<td>3 (2.3)</td>
<td>0 (0.0)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Striae Rubrae</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Flushing</td>
<td>1 (0.8)</td>
<td>0 (0.0)</td>
<td>1 (0.8)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Fluid Retention</td>
<td>2 (1.6)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Mood Change</td>
<td>6 (4.7)</td>
<td>2 (1.6)</td>
<td>3 (2.3)</td>
<td>4 (3.2)</td>
</tr>
<tr>
<td>Sleep Changes</td>
<td>2 (1.6)</td>
<td>3 (2.3)</td>
<td>3 (2.3)</td>
<td>6 (4.8)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1 (0.8)</td>
<td>1 (0.8)</td>
<td>2 (1.6)</td>
<td>3 (2.4)</td>
</tr>
<tr>
<td>Acne</td>
<td>2 (1.6)</td>
<td>2 (1.6)</td>
<td>1 (0.8)</td>
<td>3 (2.4)</td>
</tr>
<tr>
<td>Hirsutism</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (0.0)</td>
<td>1 (0.8)</td>
</tr>
</tbody>
</table>

No evidence of any increase in glucocorticoid effects were observed in Budesonide MMX® versus placebo

* Number of patients with worsening from baseline to any post-baseline visit

Travis et al, DDW 2011
Symbols indicate mean plasma cortisol level for each visit for each treatment. Error bars indicate 25th and 75th percentiles. Treatments are offset for readability. Numbers at the bottom of the graph are the number of patients at each visit that had plasma cortisol levels below the lower limit of normal (5 µg/dL).

Hitting the target...BUT...
Higher efficacy, less toxicity?

SUMMARY BUDESONIDE MMX

- Head to head with systemic steroids: Not Available
- Induces higher remission rates compared to placebo
- Does not inhibit the adrenal gland in the short and long term (1 year data Available as press release)
2. Italian solutions to steroids adverse events!
Coating of oral beclomethasone dipropionate capsules with cellulose acetate phthalate enhances delivery of topically active antiinflammatory drug to the terminal ileum

D S Levine, V A Raisys and V Ainardi

BECLOMETHASONE DIPROPIONATE: colonic release
Oral BECLOMETASON in UC in combination with 5-ASA

Oral beclometasone dipropionate in the treatment of active ulcerative colitis: a double-blind placebo-controlled study

F. RIZZELLO¹, P. GIONCHETTI¹, A. D'ARIENZO², F. MANGUSO², G. DI MATTEO³, V. ANNESE⁴, D. VALPIANI⁵, T. CASETTI⁶, S. ADAMO⁷, A. PRADA⁸, G. N. CASTIGLIONE⁹, G. VAROLI⁹ & M. CAMPieri¹

![Bar chart showing remission and improvement in patients treated with beclometason + 5ASA compared to placebo + 5ASA.](chart.png)
Objective

- Compare efficacy and security of BDP versus oral prednisone

Design

- \( N = 277(168 \ ♂) \)
- UC mild-moderate.

- Arms:
  - DPB 5 mg/day for 4 w and 5 mg every other day
  - Prednisone 40 mg/day for 2 w, tapering of 10 mg every 2 weeks (8 weeks total)

- Non inferiority study

Balzano et al. (ECCO 2010)
The Beta Study results

Response: DAI < 3 points or decrease of 3 points if DAI basal > 7

N = 277

- DPB 5 mg/day for 4 w and DPB 5 mg/day for 4 w every other day N = 135
- Pd 40 mg/day for 2 w Tapering 10 mg every 2 w (8 sem) N = 142

4 weeks

Response 64.6%
Response 66.2%

Equivalent treatments

Balzano et al. (ECCO 2010)
Mean morning serum cortisol levels were assessed in 53 out of 58 patients in the BDP group and in 51 out of 61 patients in the placebo group, they were significantly decreased in the BDP group at the end of the treatment period ($P = 0.002$), but were still within the normal range. Four out of 53 BDP-treated patients (7.5%) showed levels less than the lower reference limit of 5 $\mu g/dL$, but no signs of pituitary-adrenal function depletion, such as leg oedema or Cushing-like syndrome were observed.

Reduction in plasma cortisol level remains within the normal range, without any sign of HPA axis depletion.
Hitting the target…BUT…
Higher efficacy, less toxicity?

SUMMARY Beclomethasone dipropionate

- Head to head with systemic steroids Available
- Equal efficacy with 5-ASA or oral steroids
- Limited data on the safety profile in the short term
3. Italian solutions to steroids adverse events!
ERYTHROCYTES-MEDIATED DELIVERY OF LOW DOSES OF DEXAMETHASONE

1. Pre-swelling
2. Lysed erythrocytes
3. Concentrated red cell lysate
4. Addition of Dex 21-P

Dideco Compact Red Cell Loader
Sorin Group, Mirandola, Italy
Results

A
DEE

B
Predni

C
Sham

T4
Clinical

T8
remission

T8
Endoscopic
Remission

Annese V, AJG 2008
### Adverse events

<table>
<thead>
<tr>
<th></th>
<th>GROUP A - DEE (n=20)</th>
<th>GROUP B - PREDNI (n=10)</th>
<th>GROUP C - SHAM (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever (1 pt)</td>
<td></td>
<td></td>
<td>None</td>
</tr>
<tr>
<td>(1 day, max 38.2 °C)</td>
<td></td>
<td>Acne (8 pts)</td>
<td>None</td>
</tr>
<tr>
<td>Weight gain (5 pts)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hirsutism (2 pts)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Amenorrhea (2 pts)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia 1 case</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Annese V, AJG 2008
Hitting the target…BUT…
Higher efficacy, less toxicity?

SUMMARY ERYTHROCYTES-MEDIATED DELIVERY OF LOW DOSES OF DEXAMETHASONE

• Head to head with systemic steroids Available
• Equal efficacy
• “Fantastic” safety profile in the short term: more studies needed
Summary: have steroids had their day?

- Steroids are alive even in the biologic era (and thriving!)
- New formulations hit the “organ target” and provide overall, a better safety profile by reducing side effects and improving compliance
- Efficacy is overall similar
Summary: have steroids had their day?

- Steroids are alive even in the biologic era (and thriving!)
- New formulations hit the target and provide overall, a better safety profile by reducing side effects and improving compliance
- Efficacy is overall similar
  - (Italians like investigating new steroid formulations)