Budesonide for ulcerative colitis

Falk Symposium 147

A. S. Peña
Immunogenetics, Pathology & Gastroenterology VUMC
Amsterdam, the Netherlands
Percentage of patients with involvement of colonic segment at diagnosis

Both, H. Scand J Gastroenterol 1983
On the treatment of ulcerative colitis

"The colon should be irrigated every day

... the best is albargin, a preparation of silver nucleinate.

The English stocks were finally exhausted towards the end of 1915. I then tried silver nitrate again, but it caused too much pain

..I finally employed tannic acid as the best substitute for albargin....

This proved more effective than plain saline solution...."

Sir Arthur Hurst 1935
The first topical effective drugs

The first topical drugs which were used and proved to be highly effective in the induction of remission of ulcerative colitis were the corticosteroids.

They were introduced in England by Truelove (1958) and Watkinson (1958), and in North America by Kirsner et al., (1959).
Budesonide

- High affinity to receptor/High Potency
  - Hydrocortisone = 9; 6-Methylprednisolone = 42
  - Dexamethasone = 100; Budesonide = 935
- High first-pass hepatic metabolism
- Low systemic availability
  - Hydrocortisone = 58%; 6-Methylprednisolone = 65%
  - Dexamethasone = 62%; Budesonide = 10%

High Local Potency

Oral Topical Therapy “a model of targeted therapy”

Low Systemic Potency
Principal characteristics

Efficacy similar to that of conventional steroids but with few adverse events

significantly less impact on the hypothalamic-pituitary-adrenal axis

The Danish Budesonide Study Group Scand J Gastroenterol 1991
Budenofalk® 3mg capsules with pH-modified release of Budesonide

Hard gelatine capsule (soluble in gastric juice)

Eudragit coating resistant up to pH < 6.4

Budesonide drug-layer

Matrix: sugar pellets
EVALUATION OF ORAL BUDERSONIDE IN THE TREATMENT OF ACTIVE DISTAL ULCERATIVE COLITIS

Jeroen J. Kolkman¹, Helmut W. Möllmann², Anja Clara Möllmann³, Amado Salvador Peña⁴, Roland Greinwald⁵, Horst-Dietmar Tauschel⁵ and Guenther Hochhaus³

Amsterdam, Enschede, Zwolle, Den Helder (NL)
University of Gainsville, Florida and Dr. Falk Pharma GmbH in Freiburg

Drugs of Today 2004, 40 (7): 589-601
Single and multiple oral dosing of Budenofalk® 3 mg

- to obtain pharmacokinetic data
- Safety
- clinical efficacy

Drugs of Today 2004, 40 (7): 589-601
Methods

Patients were randomly assigned
3x3 mg budesonide per day (n = 8, Group A) or
1x9 mg budesonide per day (n = 7; Group B)
for 8 weeks or for 4 weeks in case of remission after this treatment period, respectively.
On days 5/6 the patients were hospitalized to perform the pharmacokinetic run by taking blood samples over 24 hours.
On day 0 (pre-treatment day/baseline) and on day 56 (8 weeks of treatment) biopsy specimens were taken from the descending colon, the sigmoid colon and the rectum.
Mean serum concentration of Budesonide on day 5 of the treatment

Group A (3 x 3 mg/d)

Group B (1 x 9 mg/d)

Drugs of Today 2004, 40 (7): 589-601
<table>
<thead>
<tr>
<th>pH-modified release capsules</th>
<th>3x3 mg a day in 8 patients</th>
<th>1x9 mg a day in 7 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC0-24h (ng/xh/ml)</td>
<td>13.1 (6.2)</td>
<td>27.6 (14.9)</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>3.4 (0.5)</td>
<td>5.4 (2.8)</td>
</tr>
<tr>
<td>Absolute bioavailability</td>
<td>9.7</td>
<td>18.9</td>
</tr>
</tbody>
</table>
Mean (SD) serum cortisol concentrations on day 5 of daily administration of Budesonide

Drugs of Today 2004, 40 (7): 589-601
CAI <4 or 30% decrease in CAI

Table VI: Rates of response and improvement after treatment with 3 x 3 mg (group A) or 1 x 9 mg (group B) budesonide daily on days 28 and 56.

<table>
<thead>
<tr>
<th>ITT analysis (n = 15)</th>
<th>Number of patients</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Response n (%)</td>
<td>Day 28</td>
<td>Day 56</td>
<td>Improvement n (%)</td>
<td>Day 28</td>
</tr>
<tr>
<td>Group A:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 x 3 mg/d budesonide (n = 8)</td>
<td>0</td>
<td>3 (38%)</td>
<td></td>
<td>0</td>
<td>3 (38%)</td>
</tr>
<tr>
<td>Group B:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 x 9 mg/d budesonide (n = 7)</td>
<td>4 (57%)</td>
<td>4 (57%)</td>
<td></td>
<td>4 (57%)</td>
<td>5 (71%)</td>
</tr>
<tr>
<td>p-value*</td>
<td></td>
<td>0.026**</td>
<td>0.619</td>
<td></td>
<td>0.026**</td>
</tr>
</tbody>
</table>

* Fisher's exact test, two-sided.
**Statistically significant.
Budesonide mean concentration in biopsy specimens on day 56

Drugs of Today 2004, 40 (7): 589-601
Mean clinical activity index (CAI) on day 56 after administration of oral Budesonide.
Pharmacokinetic Conclusions

The single dose of 1 x 9 mg showed a greater efficacy than the multiple applications of 3x3m budesonide pH-modified release capsules. The active drug from both dosage regimens of the budesonide pH-modified release capsules is effective in the whole colon, reaching even far distal gut regions.
Clinical conclusions

- A daily dose of 9 mg Budenofalk® was well tolerated
- Significantly improved the symptoms
- Allowed for sparing for sparing conventional, systemically acting steroids
Enemas for topical therapy

- Enemas have the advantage of treating proctitis and left-sided disease locally because they may reach the splenic flexure.

- Unfortunately, conventional steroid enemas may have unwanted glucocorticosteroid side effects because of high systemic exposure.

Pharmacokinetics and retrograde colonic spread of budesonide enemas in patients with distal ulcerative colitis

- Measurement sections of the colon-Gamma camera registrations
- Nyman-Pantelidis et al. 1994
<table>
<thead>
<tr>
<th>Patient No</th>
<th>Low viscosity</th>
<th>High viscosity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Registration times (h)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>4</td>
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<tr>
<td>5</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>6</td>
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</tbody>
</table>
Budesonide Enema for the Treatment of Active, Distal Ulcerative Colitis and Proctitis: A Dose-Ranging Study

Stephen B. Hanauer et al.

Gastroenterology 1998;115:525-532
The primary definition of remission

- Three or less bowel movements per day
  - no blood in stools
  - no symptoms of urgency, abdominal pain, or painful evacuations
- Sigmoidoscopy inflammation grade score of 0
- Patients had to achieve all of these criteria for the 2 days preceding the visit
Efficacy and safety of three doses of budesonide enema vs. placebo enema

Double-blind multicenter trial, 233 patients were randomized to receive either a placebo enema or budesonide enema at a dose of 0.5 mg/100 ml, 2.0 mg/100 ml, or 8.0 mg/100 ml.

Once daily at bedtime for 6 weeks in the treatment of active distal ulcerative colitis.

**Sigmoidoscopic inflammation grade**

- Budesonide enema at 2.0 mg significantly improved sigmoidoscopic inflammation after 4 weeks and 6 weeks.
- Budesonide enema at 8.0 mg significantly improved sigmoidoscopic inflammation after 2, 4, and 6 weeks.

***P 0.001 vs. placebo

**P 0.010 vs. placebo
Budesonide enema

- Budesonide enema is both effective and safe for the treatment of active distal ulcerative colitis/proctitis.

- A dose of 2.0 mg/100 ml is the lowest effective dose.
Budesonide foam versus hydrocortisone acetate foam in the treatment of active ulcerative proctosigmoiditis

Bar-Meir, Fidder, Faszczyk, Bianchi Porro, Sturniolo, Mickisch, Müller, Greinwald, Chowers, Groß and The International Budesonide Study Group

Bar-Meir et al Dis Colon Rect 2003
GCS Foams in proctosigmoiditis

- 248 patients
- Budesonide 2 mg
  - 120 patients
- Hydrocortisone 100mg
  - 128 patients

- 38 centers: Israel, Germany and Italy
- patients randomized to 8-weeks treatment with budesonide foam or hydrocortisone acetate foam
- once daily in the evening

Bar-Meir er al Dis Colon Rect 2003
### PP Analysis

<table>
<thead>
<tr>
<th></th>
<th>Budesonide Foam</th>
<th>Hydrocortisone Foam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical remission at week 8 (LOCF)</td>
<td>55%</td>
<td>51%</td>
</tr>
<tr>
<td>Difference (95% CI) between groups</td>
<td>4%</td>
<td>(−10.6% to 18.6%)</td>
</tr>
</tbody>
</table>

Bar-Meir et al. Dis Colon Rect 2003
This trial demonstrates a similar efficacy and safety of the two foams in patients with proctosigmoiditis.

<table>
<thead>
<tr>
<th></th>
<th>Budesonide Foam</th>
<th>Hydrocortisone Foam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical (CAI ≤ 3)</td>
<td>53%</td>
<td>52%</td>
</tr>
<tr>
<td>Endoscopic</td>
<td>59%</td>
<td>50%</td>
</tr>
<tr>
<td>Histologic</td>
<td>48%</td>
<td>50%</td>
</tr>
<tr>
<td>Subjective</td>
<td>63%</td>
<td>63%</td>
</tr>
</tbody>
</table>

Bar-Meir et al. Dis Colon Rec 2003
# Budesonide Foam vs Budesonide enema in proctosigmoiditis

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosage</th>
<th>Clinical Remission</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Budesonide Foam</td>
<td>2 mg/25ml</td>
<td>59.52%</td>
<td>P = 0.0236</td>
</tr>
<tr>
<td>Budesonide enema</td>
<td>2 mg/100ml</td>
<td>65.69%</td>
<td></td>
</tr>
<tr>
<td>Placebo enema</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo foam</td>
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</tbody>
</table>

- 449 patients per PP
- 83.6% of the patients preferred the foam

- Double-blind, double-dummy, randomized for 28 days treatment
- Centers: Germany, Israel, Latvia, Lithuania, Hungary

Gross, V et al DDW Gastroenterology 2004;126:A-465
The future of budesonide in ulcerative colitis

- Larger studies are indicated
- Improvement in budesonide quantitative method in intestinal tissue needs attention
- However, for left-sided colitis a topical application in the form of a foam remains the therapy of choice
Conclusions

- Evidence
- The need for large trials
- Which outcomes should we measure?
- Getting evidence into practice