Practical Use of Steroids In IBD

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Steroids In IBD

• Ulcerative colitis
  – Rectal
    • Conventional steroids
    • Budesonide
  – Oral
  – IV

• Crohn’s Disease
  – Oral conventional steroids
  – Oral budesonide
Corticosteroid Pharmacokinetics

- **SYSTEMIC GLUCOCORTICOIDS**
- **TOPICAL GLUCOCORTICOIDS**

<table>
<thead>
<tr>
<th>Corticosteroid</th>
<th>Clearance (L/h)</th>
<th>Oral Bioavailability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisolone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexametasone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triamcinolone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Budesonide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flunisolide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluticasone</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **CLEARANCE (L/h)**
- **ORAL BIOAVAILABILITY (%)**
Summary of Human Pharmacokinetics of Budesonide when Applied to Bowel Mucosa

- 10% intact budesonide
- 90% first pass metabolism in liver
- 90% metabolites of low GCS potency

To systemic distribution

Orally administered budesonide (controlled ileal release)

Rectally administered budesonide (enema)
Sidney Truelove, Green College, Oxford University, 1996
## Rectal Administration of Systemically Active Corticosteroids for Mildly to Moderately Active UC

<table>
<thead>
<tr>
<th>Study</th>
<th>Number</th>
<th>Duration</th>
<th>Steroid</th>
<th>Remission</th>
<th>Steroid</th>
<th>Placebo</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Truelove</td>
<td>40</td>
<td>1 wk</td>
<td>hydrocortisone</td>
<td>100 mg</td>
<td>55%</td>
<td>5%</td>
<td>0.01</td>
</tr>
<tr>
<td>Lennard-Jones</td>
<td>39</td>
<td>3 wk</td>
<td>prednisolone</td>
<td>5 mg</td>
<td>56%</td>
<td>9%</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Jones</td>
<td></td>
<td></td>
<td></td>
<td>100 mg</td>
<td>90%</td>
<td>11%</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

Meta-Analysis of Conventional Corticosteroid Enemas versus 5-ASA Enemas for Induction of Symptomatic Remission in Active Distal UC

Corticosteroids better

Odds ratio

5-ASA better


CP985036-11
# Budesonide Enemas for Mildly to Moderately Active UC

<table>
<thead>
<tr>
<th>Study</th>
<th>Number</th>
<th>Duration</th>
<th>Budesonide</th>
<th>Remission</th>
<th>Placebo Remission</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hanauer</td>
<td>233</td>
<td>6 weeks</td>
<td>0.5 mg</td>
<td>7%</td>
<td>4%</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.0 mg</td>
<td>19%</td>
<td>4%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8.0 mg</td>
<td>27%</td>
<td>4%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Hanauer. Gastroenterology 1998
Meta-Analysis of Conventional Corticosteroid Enemas versus Budesonide Enemas for All Outcomes in Active Distal UC

**Improvement**
- Symptomatic (n=1)
- Endoscopic (n=4)
- Histological (n=4)

**Remission**
- Symptomatic (n=2)
- Endoscopic (n=4)
- Histological (n=2)

Pooled odds ratio: Conventional corticosteroids better vs. Budesonide better.
Effect of Budesonide and Prednisolone Enema on Mean Morning Plasma-Cortisol Levels

Lofberg: Aliment Pharmacol Ther, 1994
Oral Cortisone: Mild-to-Severe Active Ulcerative Colitis: Clinical Response and Remission at 6 Weeks

Clinical response Clinical remission

Placebo (n=101) Cortisone (n=109)

Percent of Patients

P<0.001

41 69

61 16

P<0.001

*Clinical remission defined as 1 or 2 stools/day without blood
†Clinical response defined as improved or clinical remission

Oral Cortisone: Mild-to-Severe Active Ulcerative Colitis: Mucosal Healing at 6 Weeks

*Defined as normal or near normal (slight hyperemia or granularity) mucosa

Prednisone Dose Response in UC

- 60 mg daily
- 40 mg daily
- 20 mg daily

Prednisolone:
Mild-to-Severe Active Ulcerative Colitis

Improvement  †

- Prednisolone 10 mg qid: 77%
- Prednisolone 40 mg q day: 74%

Remission  *

- Prednisolone 10 mg qid: 23%
- Prednisolone 40 mg q day: 13%

†Defined as a decrease in the Powell-Tuck index score ≥ 2 points
*Defined as a Powell-Tuck index score of 0

## Corticosteroid Maintenance Therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Indication</th>
<th>Steroid</th>
<th>Response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lennard-Jones</td>
<td>Maintenance</td>
<td>Prednisone</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15 mg</td>
<td>40</td>
</tr>
</tbody>
</table>

IV Prednisolone 60 mg in Severely Active UC: Clinical Response

Clinical response defined as improved or clinical remission

Truelove. Lancet. 1974
Mortality from a severe attack of Ulcerative Colitis

Corticosteroids introduced in 1952
Immediate and Prolonged Outcomes of Corticosteroid Therapy* in UC

30-Day Responses (n=63)
- Complete: 54% (n=34)
- Partial: 30% (n=19)
- None: 16% (n=10)

1-Year Responses (n=63)
- Steroid Dependent: 22% (n=14)
- Prolonged Response: 49% (n=31)
- Surgery: 29% (n=18)

Prednisone For Induction of Remission

- **Prednisone**
  - CDAI <150: 0.25 mg/kg (17.5 mg/70 kg)
  - CDAI 150-300: 0.5 mg/kg (35 mg/70 kg)
  - CDAI >300: 0.75 mg/kg (52.5 mg/70 kg)

- **Placebo**

60% vs 30%
P<0.0001

Prednisone Therapy For Maintenance of Remission


Prednisone 1/4 mg/kg (20 mg)
Placebo

Months After Randomization

Patients (%)
Immediate and Prolonged Outcomes of Corticosteroid Therapy in Crohn’s Disease

30-Day Responses (n=74)

- Complete: 58% (n=43)
- Partial: 26% (n=19)
- None: 16% (n=12)

1-Year Responses (n=74)*

- Steroid dependent: 32% (n=24)
- Prolonged response: 28% (n=21)
- Surgery: 38% (n=28)

*One patient lost to follow-up

Budesonide for Active Crohn’s Disease

Patients in Remission (%)

<table>
<thead>
<tr>
<th>Group</th>
<th>2 wk</th>
<th>4 wk</th>
<th>8 wk</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>11</td>
<td>17</td>
<td>21</td>
<td>0.13</td>
</tr>
<tr>
<td>n = 66</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 mg Placebo</td>
<td>10</td>
<td>25</td>
<td>33</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>n = 67</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 mg Budesonide</td>
<td>33</td>
<td>36</td>
<td>51</td>
<td>&lt;0.009</td>
</tr>
<tr>
<td>n = 61</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 mg Budesonide</td>
<td>28</td>
<td>42</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>n = 64</td>
<td></td>
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</tbody>
</table>

Budesonide 9 mg/day versus Mesalamine 4 g/day for Active Crohn’s Disease


<table>
<thead>
<tr>
<th>Weeks of Treatment</th>
<th>Patients in Remission (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Budesonide: 40% Mesalamine: 40%</td>
</tr>
<tr>
<td>4</td>
<td>Budesonide: 50% Mesalamine: 50%</td>
</tr>
</tbody>
</table>
| 8                 | Budesonide: 70% Mesalamine: 70% *
| 12                | Budesonide: 60% Mesalamine: 60% †
| 16                | Budesonide: 60% Mesalamine: 60% ‡

*p=0.001; †p=0.004; ‡p<0.001.

Budesonide for Crohn’s Disease: Remission Maintenance

A Pooled Analysis of 4 Placebo-Controlled Trials of Budesonide Maintenance Treatment in Crohn’s Disease: Time to Relapse

Placebo 3 mg BUD 6 mg BUD

Median Time to Relapse (Days)

P = .0072 across all 3 treatments
P = .0024 placebo vs 6 mg budesonide
P = .28
P = .058

156 days
170 days
268 days

BUD = budesonide
A Pooled Analysis of 4 Placebo-Controlled Trials of Budesonide Maintenance Treatment in Crohn’s Disease: Time to Relapse (cont’d)

Budesonide 6 mg vs Placebo in Steroid-Dependent Crohn’s Disease

Budesonide 6 mg versus Mesalamine 3 g in Steroid-Dependent Crohn’s Disease

log-rank test, 8.6; P < 0.005

Bone Mineral Density In Relation To Budesonide And Prednisolone

Corticosteroid Toxicity

- Moon face
- Acne
- Ecchymoses
- Hypertension
- Hirsutism
- Petechial bleeding
- Striae

- Diabetes
- Infection
- Osteonecrosis
- Osteoporosis
- Myopathy
- Cataracts
- Glaucoma
- Psychosis
Infections and mortality in the TREAT registry: 15,000 patient-years of experience

Multivariate analysis

<table>
<thead>
<tr>
<th></th>
<th>Mortality</th>
<th>Serious infections</th>
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</thead>
<tbody>
<tr>
<td>IFX</td>
<td>1.5</td>
<td>2.0</td>
</tr>
<tr>
<td>AZA</td>
<td>1.1</td>
<td>1.3</td>
</tr>
<tr>
<td>6-MP</td>
<td>0.8</td>
<td>0.9</td>
</tr>
<tr>
<td>MTX</td>
<td>0.7</td>
<td>0.8</td>
</tr>
<tr>
<td>Steroids</td>
<td>0.5</td>
<td>0.6</td>
</tr>
</tbody>
</table>

* \( p=0.001 \)
** \( p<0.0001 \)

IFX = infliximab; AZA = azathioprine; MTX = methotrexate

Lichenstein GR, et al. Gastroenterology 2006;130(suppl 4):A-71
## Side Effects of CIR Budesonide and Prednisolone in Patients With Active Crohn’s Disease

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Budesonide</th>
<th>Prednisolone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moon face</td>
<td>17%</td>
<td>35%</td>
</tr>
<tr>
<td>Acne</td>
<td>6%</td>
<td>23%</td>
</tr>
<tr>
<td>Swollen ankles</td>
<td>2%</td>
<td>11%</td>
</tr>
<tr>
<td>Easy bruising</td>
<td>2%</td>
<td>7%</td>
</tr>
<tr>
<td>Hirsutism</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Buffalo hump</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td>Skin striae</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Other</td>
<td>9%</td>
<td>16%</td>
</tr>
<tr>
<td>Total</td>
<td>40%</td>
<td>98%</td>
</tr>
</tbody>
</table>

Conclusions

- Conventional steroids and budesonide are highly effective as induction agents in patients with ulcerative colitis and Crohn’s disease.
- These agents are not effective as maintenance therapy.
- Steroid dependence is frequent.
- Serious toxicity is associated with conventional steroids including an increased risk of mortality.
- The use of conventional steroids is likely to decrease in future years.
- Oral budesonide has significantly less steroid side effects than conventional steroids.