GLUCOCORTICOSTEROIDS
FOR
INFLAMMATORY BOWEL DISEASE

Falk Symposium # 159, Istanbul May 4-5, 2007
GCS in IBD

- 1:st line treatment in mod./sev. UC and CD
- Broad anti-inflammatory effects
- Rapid onset of action
- Unsurpassed efficacy
- Readily available
- Easily administered
- Generally well tolerated
- Recognized toxicity profile
- Relatively inexpensive
Glucocorticosteroids

Array of anti-inflammatory actions:

- Antigen presentation
- WBC-recruitment, migration
- Pro-inflammatory cytokines
- NO/iNOS
- NFκB p65

Apoptosis of immune cells

Anti-inflammatory cytokines
First DB, RCT in active ulcerative colitis

SC Truelove
Oxford, UK

Remission

50 %

41 %

n=109

Cortisone

Truelove & Witts, BMJ 1955

16 %

n=101

Placebo

25 %

0
Dosing of GCS

UC – moderately active attacks:
• (20) - 40 - (60) mg of oral prednisolone/day
• 40 mg o.m.
  optimal dose based on efficacy/practical considerations/AE

Baron et al, BMJ 1967
Powell-Tuck et al, Scand J Gastroenterol 1978

UC - severe attacks:
• Intensive i.v. regimen
• Hydrocortisone 200-400 mg/day, betamethasone 6-16 mg/day
  (+ GCS in enema, or rectal drip)

• Overall results: 60 % remission/15 % improvement

• Pancolitis: 47 % remission. Extensive/distal UC: 88 %
  Jämerot et al, Gastroenterology 1985
Prednisone in active CD


Remission, CDAI <150

Prednisone

P=0.017

Placebo

Patients (%)
Ileocolonic Crohn’s disease:

- Prednisolone/prednisone:
  40 mg o.m./d (ca 0.5 mg/kg)
  60-82 % remission rate at 17-18 weeks.

  RCT: NCCDS + ECCDS, Gastroenterology 1979 + 1984

- High-dose prednisolone (1 mg/kg/d):
  80-92 % symptomatic remission (=CDAI<150)
  27 % endoscopic remission rate

  Prospective, open study: Getaid, Gastroenterology 1992

- Do not use in fibrostenotic disease, post op diarrhoea, fistulizing CD, septic complications (eg. abdominal abscess)
Increased risk of infections and mortality in TREAT-registry

**Multivariate analysis**

*\( p=0.001 \); **\( p<0.02 \)

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
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<tbody>
<tr>
<td>IFX</td>
<td>2.5</td>
</tr>
<tr>
<td>AZA 6-MP MTX</td>
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</tr>
<tr>
<td>Steroids</td>
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</tr>
<tr>
<td>Serious infections</td>
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<tr>
<td>Steroids Narcotics</td>
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Lichtenstein et al. Gastroenterology 2005;128 (suppl 2): A580
Problems with conventional GCS

- Steroid refractory disease
- Steroid dependency
- Adrenal gland suppression
- Metabolic consequences (glucose tolerance, bone metabolism etc)
- Systemic side-effects (DM, osteopenia/-porosis, hypertension, etc)
- Symptomatic/cosmetic AE (insomnia, mood-swings, weight, acne, etc.)
- Improved GCS-profile possible…?
Receptor binding affinity of GCS-compounds

<table>
<thead>
<tr>
<th>Compound</th>
<th>Affinity</th>
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<tbody>
<tr>
<td>Hydrocortisone</td>
<td>9</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>16</td>
</tr>
<tr>
<td>6-Methylprednisolone</td>
<td>42</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>100</td>
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<tr>
<td>Budesonide</td>
<td>935</td>
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Budesonide

- Non-halogenated gcs
- High topical activity - proven in asthma
- Lipophilic – well absorbed
- 80-90 % first-pass metabolism in liver via Cytochrome P-450 III system
- Low systemic load
- Ideal for topical use in IBD
- Developed for IBD by:
  
  *Astra Zeneca, Dr. Falk Pharma, Cosmo*
Budesonide enema/foam in active distal UC

• Superior to placebo given at bedtime for 4-8 weeks.
  *Danielsson A et al, ScJ Gastro 1987*

• 2 mg/100 ml optimal dose.
  *Hanauer et al, Gastroenterology 1998*

• Equivalent to conv. GCS-enemas/foams (HC, pred)

• Equivalent to 5-ASA enema
  *Lamers et al, Gastro 1991 (A), Lemann et al, APT1995*

• Bud-foam preferred comp. to enema (n=251) *Gross V, et al. APT 2006*
Controlled Ileal Release budesonide 9 mg vs. prednisolone 40 mg for active CD


Fewer and less severe GCS AEs in budesonide group (P=0.003).
Serious septic AEs in prednisolone group.
DB, RCT with oral budesonide CIR in active CD

P-Cortisol suppression (n=178)

Budesonide
4.5 mg b.i.d
9 mg o.m.

Prednisolone
40 mg o.m.

Campieri et al, Gut 1997
Budesonide 9 mg/d vs. 5-ASA 4 g/d

<table>
<thead>
<tr>
<th>Time (w)</th>
<th>Budesonide</th>
<th>5-ASA (Pentasa)</th>
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<tbody>
<tr>
<td>2</td>
<td>40</td>
<td>30</td>
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<tr>
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<tr>
<td>16</td>
<td>100</td>
<td>90</td>
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</table>

Budesonide had significantly fewer and less severe AEs

Cochrane review of oral budesonide for CD

8 RCT Entocort® (AstraZeneca) Controlled Ileal Release
Budenofalk® (Dr. Falk) Eudragit-covered

EFFICACY:

- Budesonide superior vs. placebo (OR: 2.85, CI 1.67-4.87) (2)
- Superior vs. mesalazine 4g (OR: 2.80, CI 1.50-5.20) (1)
- Inferior vs. prednisone/-lone (OR: 0.69, CI 0.51-0.95) (5)

SAFETY:

- No difference vs. placebo (OR: 0.98, CI 0.58-1.67)
- Fewer AEs vs. GCS (OR: 0.38, CI 0.28-0.53)

1 yr follow-up after GCS-therapy in CD


Responders to GCS therapy

Remission 44%

GCS-dep. 36%

GCS-refr. 20%
**Budesonide for steroid-dependent CD**

**SWITCH:**
Prednisolone dep. patients (CDAI < 200, n=120), DB, RCT
Tapering of pred. to zero,
Budesonide 6 mg vs. placebo for 12 w.

- Relapse rate after 12 w: 32 % vs. 65 % (P<0.001)
  
  *Cortot A et al, Gut 2001*

**GREEK STUDY:**
Non-Aza treated patients in remission (refused/intol, n=57):
Randomised to 6 mg budesonide/d vs. 5-ASA 3g/d

- Relapse rate at 1yr: 55% vs. 82% (P=0.045)
  
Maintenance of remission in ileocecal CD

Pooled analysis of 4 RCTs, n=380

Cumulative probability of remission

- Placebo
- Budesonide 6 mg
- Budesonide 3 mg

Days

P<0.005

Topical GCS for IBD – the way forward

• Targeted release preparations for colonic IBD?
Oral budesonide CCR (10 mg) vs. prednisolone (40 mg) in active extensive and left-sided UC (n=72):

Löfberg et al, Gastroenterology 1996
Budesonide for UC in MultiMatrixSystem (MMX)

- pH - gastroprotective layer
- hydrophilic matrix
- combined Eudragit L/S

- Sustained colonic delivery

PII-study:
Active UC, n=32
9 mg/d vs placebo for 4 w:

CAI-improvement:
43% vs. 25 % (P<0.0001)

No diff. in p-cortisol/ACTH-test

d’Haens el al, DDW 2007
Prednisolone metasulphobenzoate (PMSBS) coated with COLAL (Ethylcellulose + glassy amylose starch cover)

NO STEROID RELATED AEs - NO CHANGE IN CORTISOL LEVELS
Topical GCS for colonic IBD

• Combination of oral and rectal formulations?
Topical GCS for IBD

• New indications
Oral budesonide for microscopic colitis

- **Cochrane analysis:**
  - 3 studies in collagenous colitis.
  - OR for response to treatment with budesonide: 12.32 (CI 5.53-27.56)
  - NNT=2

- **Long-term management?**
- **Mechanisms:**
  - Downregulation of iNOS? Decrease in Bile Acid malabsorption?

From Bonderup et al, UEGW 2001

Budesonide applications for various IBD-situations

• New oral preparation of budesonide in active distal UC

• Oral budesonide of value in refractory pouchitis
  Gionchetti et al, APT 2007

• Budesonide CIR as good as pred. for joint pain in CD – 74 % remission
  Florin THJ et al, Clin Exp Pharmacol 2000

• Efficacious for treatment of lymphocytic colitis
  Lazenby AJ, Sem Diagn Pathol 2005

• Decreases high output from ileostomies in CD-pat
  Ecker et al. D C R 2005

• Budesonide foam as efficacious as metronidazole in active pouchitis
  Sambuelli A et al, APT 2002
Topical GCS
Long-term toxicity incl. impact on bone-turnover?

"Budesonide is associated with better preserved bone mass compared with prednisolone in only the GCS-naive patients with active ileocecal CD"

Schon AJ el, J Clin Gastro Hepatol 2005
GCS in IBD

• Unsurpassed, high efficacy

• AE profile well known

• Potentially hazardous AEs

• Cave! *Long-term treatment/septic complications*

• Budesonide in oral and rectal forms:
  
  *Established in several IBD-conditions*
  *Improved AE-profile*