Therapy of IBD: Step up or top down?

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• What is *STEP-UP* and *TOP-DOWN* therapy?

• The natural course of Crohn’s disease
  • need for steroid treatment
  • need for operation

• Can we induce a structural improvement (mucosal healing) and what does it mean.
Current therapies in autoimmune diseases can not reverse the sequelae once they occur:
- Fibrotic strictures in Crohn’s disease
- Joint damage in RA

Early intervention may prevent irreversible damage and lead to higher long term remission.

In RA combination therapy better [biologic therapy + immunosuppressive therapy (MTX)] better than monotherapy.
Top-down therapy in RA - Clinical remission

Study population 799 RA patients: Dx RA < 3 years, no MTX
Prospective placebo controlled study

* \( p < 0.001 \) vs. Adalimumab alone or MTX alone

Breedveld et al. 2006
Top-down therapy in RA - inhibition of radiological progression

*Sharp Score: Radiological Score scale 0-398

*Breedveld et al. 2006

*p< 0.001 vs Adalimumab alone or MTX alone, §p<0.001 vs MTX alone
Anti-TNF antibody therapy in rheumatoid arthritis - Risk for serious infections and malignancies

- Meta-analysis of 9 trials
- 3493 patients receiving adalimumab (5) or infliximab (4) > 12 weeks
  - Low dose: ≤3 mg/kg infliximab q4 weeks or 20 mg adalimumab q1 week
  - High dose: ≥6 mg/kg infliximab q8 weeks or 40 mg adalimumab q2 weeks
- 1512 patients receiving placebo only (2) or methotrexate (6) or DMARD (1)

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Odds Ratio (95% confidence interval)</th>
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<tbody>
<tr>
<td></td>
<td>All doses anti-TNF vs placebo</td>
</tr>
<tr>
<td>≥ 1 malignancy</td>
<td>3.3 (1.2-9.1)*</td>
</tr>
<tr>
<td>≥ 1 serious infection</td>
<td>2.0 (1.3-3.1)*</td>
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* significant

Bongartz et al. 2006
232 Patients underwent either “radical” or “nonradical” surgery. “Radical”: no visible lesion left behind.

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<thead>
<tr>
<th></th>
<th>“Radical”</th>
<th>“Nonradical”</th>
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<tbody>
<tr>
<td>Previous surgery (%)</td>
<td>40</td>
<td>41</td>
</tr>
<tr>
<td>Ileum and colon involved (%)</td>
<td>94</td>
<td>92</td>
</tr>
<tr>
<td>Recurrence 1 year (%)</td>
<td>64 *</td>
<td>47</td>
</tr>
<tr>
<td>2 years (%)</td>
<td>47 *</td>
<td>27</td>
</tr>
<tr>
<td>3 years (%)</td>
<td>24</td>
<td>11</td>
</tr>
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* = significant

Ewe et al. 1989
Open label, randomized trial, active CD (CDAI >200) newly diagnosed or active <4 years without steroid or immunosuppression

**Step up** (n=64)

- Steroids
- +AZA
- +IFX

**Top down** (n=65)

- IFX (week 0, 2, 6)
- + AZA
- AZA + IFX
- AZA + IFX + Steroids

Hommes et al. DDW 2006
The Step-up versus Top-down trial

CDAI < 150 and no surgery and no steroids

*significant

Hommes et al. DDW 2006
## The Step-up versus Top-down trial

### Proportions of patients on immunosuppression

<table>
<thead>
<tr>
<th></th>
<th>Top-down; n=65</th>
<th>Step-up; n=64</th>
</tr>
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<tbody>
<tr>
<td>Week 52</td>
<td>100%</td>
<td>74%</td>
</tr>
<tr>
<td>Week 104</td>
<td>94%</td>
<td>77%</td>
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### Mean number of days of steroid treatment

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<tr>
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<th>Until week 52</th>
<th>Until week 104</th>
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<tbody>
<tr>
<td>Top-down; n=65</td>
<td>0.5</td>
<td>6</td>
</tr>
<tr>
<td>Step-up; n=64</td>
<td>70</td>
<td>80</td>
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No significant difference in adverse events (but 1 stomach cancer in the Top-down group)
The natural course of IBD
STEROIDS FOR IBD – POPULATION RELATED DATA

**CD**
- **n = 173**
- Steroids: **n = 74 (43%)**
  - CR: 43 (58%)
  - PR: 19 (26%)
  - NR: 12 (16%)
- Inception cohort **1970 - 1993**
- Surgery: 28 (38%)
- Remission: 24 (32%)
- Steroid dependent: 21 (28%)

**UC**
- **n = 185**
- Steroids: **n = 63 (34%)**
  - CR: 34 (54%)
  - PR: 19 (30%)
  - NR: 10 (16%)
- Surgery: 18 (29%)
- Remission: 31 (49%)
- Steroid dependent: 14 (22%)

Faubion et al. 2001
Cumulative risk for the first intestinal resection (Stockholm County 1955-1989)

n=1424
CARD 15 mutations and timepoint of first operation

[Graph showing the proportion of patients without CD-related surgery over time for different categories of ileal disease: No Ileal Disease (Heterozygotes or Wildtypes), Any Ileal Disease (Homozygotes or Compound Heterozygotes), Any Ileal Disease (Heterozygotes or Wildtypes).]
Mucosal healing with infliximab
## Prevention of structural damage - Mucosal healing and clinical remission

<table>
<thead>
<tr>
<th>IFX week 0</th>
<th>IFX or Placebo week 2,6</th>
<th>Endoscopy week 10</th>
<th>IFX or Placebo every 8 weeks until week 46</th>
<th>Endoscopy week 54</th>
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**Accent I**

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<th>Clinical remission</th>
<th>Week 10</th>
<th>Week 54</th>
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<tbody>
<tr>
<td></td>
<td>Mucosal healing</td>
<td>No mucosal healing</td>
</tr>
<tr>
<td>Yes</td>
<td>36%</td>
<td>41%</td>
</tr>
<tr>
<td>No</td>
<td>64%</td>
<td>59%</td>
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Rutgeerts et al. 2006
Top-down therapy might be a promising approach, but...

- We need tools to better predict the course of the disease of an individual patient
  - Genetical markers (?)
  - Serological markers (?)

- More prospective studies are mandatory (do we need biologic + azathioprine/MTX?)
- Side effects vs. benefit?
INFLUENCE OF SMOKING ON THE COURSE OF CD – INTERVENTION STUDY

Cosnes et al. 2001
I’ve spent much of my career trying to avoid prescribing steroids for IBD patients...

I was wary of taking steroids...(but) within 24 hours I felt great
...much to the chagrin of my fellows who were required to keep up with me.

The only thing better than the pain relief provided by the steroids was awakening in the recovery room after surgery.