Therapy of inflammatory bowel disease:
Step up or top down?

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Therapy of IBD
Step up or top down?

"Step-up" therapy of Crohn's disease

**Therapy of IBD**
**Step up or top down?**

**ECCO Statement SH**
- Corticosteroid dependent disease should be treated with azathioprine/methotrexate [EL1a, RG A], or, if intolerant or ineffective, methotrexate should be considered [EL1a, RG A].
- In this case, addition of infliximab should be considered [EL1a, RG A], although surgical options should also be considered and discussed.

**ECCO Statement SH**
- Severe activity initially be treated with systemic corticosteroids [EL1a, RG A]. For those who have relapsed, azathioprine/methotrexate should be added [EL1a, RG B]. Or, if intolerant, methotrexate should be considered [EL1a, RG B]. Infliximab should be considered in addition for corticosteroid or immunomodulator refractory disease or intolerance [EL1b, RG A], although surgical options should also be considered and discussed.

**ECCO Statement SH**
- The benefit of mesalazine is limited [EL1a, RG B]. Antibiotics cannot be recommended [EL1b, RG A]. No treatment is an option for some patients with mild symptoms [EL5, RG D].

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Refractory to immunosuppressive therapy

Severe activity

mild to moderate activity

Chronic activity (steroid-dependent or steroid refractory)
Therapy of IBD
Step up or top down?

Disease behaviour after first steroid therapy in IBD
Crohn’s disease (n=173) and Ulcerative colitis (n=185)

- Complete response
  CD (n=43) (58%)
  UC (n=34) (54%)
- Partial response
  CD (n=19) (26%)
  UC (n=19) (30%)
- Nonresponse
  CD (n=12) (16%)
  UC (n=10) (16%)

- Prolonged response
  CD 24/74 (32%)
  UC 31/63 (49%)

- Steroid dependency
  CD 21/74 (28%)
  UC 14/63 (22%)

Prednisolone versus 6-MP as first-line therapy in children with moderate to severe Crohn’s disease

Therapy of IBD
Step up or top down?

Rates of remission in chronic active Crohn’s disease treated with TNF α-antibodies

100 % = Patients with initial response to therapy

Schreiber et al. DMW 132, 1770-1774, 2007
Azathioprine / 6-MP versus combination AZA / 6-MP + infliximab in steroid-dependent patients with active Crohn’s disease

Lemann et al. Gastroenterology 130, 1054-1061, 2006
Effect of scheduled versus episodic infliximab treatment on mucosal healing in patients with chronic active steroid-dependent Crohn’s disease

Mortality among patients with IBD 1996 - 2002

Hutfless et al. Gastroenterology 133, 1779-1786, 2007
Risk factors for opportunistic infections in patients with inflammatory bowel disease

Risk for opportunistic infection in association with specific medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>OR</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No medication</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>any medication</td>
<td>3.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mesalamine</td>
<td>1.0</td>
<td>0.94</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>3.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AZA/6-MP</td>
<td>3.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MTX</td>
<td>4.0</td>
<td>0.26</td>
</tr>
<tr>
<td>Infliximab</td>
<td>4.4</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Risk factors for opportunistic infections in patients with inflammatory bowel disease

<table>
<thead>
<tr>
<th># of immunosuppressants</th>
<th>cases (n=100)</th>
<th>controls (n=200)</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>38 (38%)</td>
<td>129 (64%)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>1</td>
<td>38 (38%)</td>
<td>59 (29%)</td>
<td>2.9</td>
</tr>
<tr>
<td>2 or 3</td>
<td>24 (24%)</td>
<td>12 (6%)</td>
<td>14.5</td>
</tr>
<tr>
<td>No medication</td>
<td>39 (39%)</td>
<td>129 (65%)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>16 (15%)</td>
<td>27 (14%)</td>
<td>2.2</td>
</tr>
<tr>
<td>AZA</td>
<td>20 (205)</td>
<td>31 (15%)</td>
<td>3.4</td>
</tr>
<tr>
<td>Infliximab</td>
<td>3 (3%)</td>
<td>2 (1%)</td>
<td>11.1</td>
</tr>
<tr>
<td>AZA + Corticosteroids</td>
<td>16 (16%)</td>
<td>6 (3%)</td>
<td>17.5</td>
</tr>
<tr>
<td>AZA + Infliximab</td>
<td>1 (1%)</td>
<td>5 (2%)</td>
<td>1.6</td>
</tr>
<tr>
<td>AZA + Steroids + Infliximab</td>
<td>5 (5%)</td>
<td>0 (0%)</td>
<td>infinite</td>
</tr>
</tbody>
</table>

Conclusion: 1) aggressive immunosuppressive therapy in combination with TNFα-blockade leads to higher remission rates in chronic steroid-dependent or refractory patients!

2) this aggressive therapy may lead to a higher risk of infection and possibly malignancy in long-term therapy!

Is a top-down combination therapy for all therapy-naive patients beneficial? What are the aims and the risks of such a therapy? How many patients are „overtreated“ with this form of therapy?
Top down therapy goal: Disease modification

Rheumatoid arthritis: Remission (ACR 70) / quality of life
Reduction of joint destruction
Therapy of IBD
Step up or top down?

„Step-up“ versus „Top down“ therapy in rheumatoid arthritis (RA) BeSt-study
data after 1 year

Goekoop-Ruiterman et al. Arthritis & Rheumatism 52, 3381-3390, 2005
Therapy of IBD
Step up or top down?

BeSt-Study - data after 2 years

ACR 70 reduction after 2 years (70% reduction)

Therapy of IBD
Step up or top down?

BeSt-Study - data after 2 years

Top down therapy  Goal: Disease modification

Crohn’s disease:
- Remission (CDAI < 150) / quality of life
- Reduction of stenosis / perforating disease
- Need for surgery, mucosal healing
Top down therapy  Goal: Disease modification

Crohn’s disease:
Remission (CDAI $< 150$) / quality of life
Reduction of stenosis / perforating disease
need for surgery, mucosal healing
Early combined immunosuppression:
  3 infusions of infliximab (5mg/kg)
  + azathioprine (2-2.5 mg/kg) if intolerant
methotrexate 25 mg s.c. weekly (15 mg p.o.)

if CDAI > 200
or increase >50 points: infliximab i.v.
prednisolone p.o.

Step-up:
Prednisolone / budesonide
  → azathioprine
  → infliximab

Top down versus bottom up in Crohn’s disease

Therapy of IBD
Step up or top down?

Top down versus bottom up in Crohn’s disease

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Top down versus bottom up in Crohn’s disease

% of patients given prednisolone

% of patients given Azathioprine / MTX

% of patients given infliximab

## Therapy of IBD
### Step up or top down?

### Top down versus step up in Crohn’s disease

#### Infections / Surgery

<table>
<thead>
<tr>
<th></th>
<th>Top down</th>
<th>Step up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Early combined immunosuppression (n=65)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Common cold</td>
<td>26 (40.0%)</td>
<td>31 (48.4%)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>22 (33.8%)</td>
<td>20 (31.3%)</td>
</tr>
<tr>
<td>Gastrointestinal infections</td>
<td>12 (18.5%)</td>
<td>13 (20.3%)</td>
</tr>
<tr>
<td>Vaginal infections</td>
<td>7 (10.8%)</td>
<td>7 (10.9%)</td>
</tr>
<tr>
<td>Urinary tract infections</td>
<td>6 (9.2%)</td>
<td>6 (9.4%)</td>
</tr>
<tr>
<td>Eye infections</td>
<td>4 (6.2%)</td>
<td>3 (4.7%)</td>
</tr>
<tr>
<td><strong>Conventional management (n=64)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>p value†</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.38</td>
<td>0.85</td>
</tr>
<tr>
<td></td>
<td>0.83</td>
<td>1.00</td>
</tr>
<tr>
<td>Surgery – resection</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Surgery fistula /</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>or perianal abscess</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 patient in the top down group suffered from demyelination

Mucosal healing top down versus step up

In 8/18 centers colonoscopy was performed at week 104 (49/133 patients)

<table>
<thead>
<tr>
<th></th>
<th>Top down (n=26)</th>
<th>step up (n=23)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>„No“ ulcers visible</td>
<td>19/26 (73%)</td>
<td>7/23 (30%)</td>
<td>0.0028</td>
</tr>
<tr>
<td>Endoscopy score</td>
<td>0.7</td>
<td>3.1</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

1) Need of a large trial comparing
2) Azathioprine / 6-MP
3) TNFα- antibody
3) Combination of both
   for 2 years regarding efficacy (remission), functional outcome (surgery, mucosal healing) side effects (infections, malignancy, autoimmunity)

SONIC trial (Study of biologic and immunomodulator naive patients in Crohn’s disease) with 500 patients is under way!
What do we still need to know or to do?

2) Need to identify patients with a benign disease course which might be overtreated with a top down concept.

3) We need alternative immunosuppressants with less infections, less immunogenicity, less fatal malignancy (adalimumab ?, certolizumab?)
F. Colombel, UEGW Paris Oktober 2007

Is it time to reverse the pyramid?

Not yet
Therapy of IBD
Step up or top down?
Metaanalyse der Wirksamkeit von Azathioprin (6-MP) zur
a) Remissionsinduktion und
b) Remissionserhaltung bei Morbus Crohn

Remissionsinduktion bei etwa 60%

Pearson et al. Azathioprine and 6-mercaptopurine in Crohn’s disease
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Azathioprine / 6-MP versus combination AZA / 6-MP + infliximab in steroid-dependent patients with Crohn’s disease

Remission and off steroids

P=0.009  P=0.03  P=0.02  P=0.08  P=0.14  P=0.16

AZA/6MP + Placebo

AZA/6MP + infliximab 5 mg/kg

Lemann et al. Gastroenterology 130, 1054-1061, 2006
Therapy of IBD
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Top-down Therapie bei Morbus Crohn – Pilotstudie Belgien

Anti-TNF + Azathioprin

+ Anti-TNF (episodisch)

Steroide

CDAI < 150 & keine Steroide

Hommes et al., Lancet 2007 (in press)
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