The step-up approach to therapy of IBD is the standard of practice

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Why did physicians consider the top down approach in CD?
No change in natural history

- Despite earlier and more widespread use of immunosuppressive therapy in the last decades,
  the cumulative need for intestinal resection has not been reduced.

- Stable percentage of 30% in the first 5 years.
Anti-TNF Therapy
Surgery and Hospitalizations

ACCENT I

Patients on maintenance of anti TNF with mucosal healing required fewer hospitalizations and surgical interventions

Gastroenterology 2004;126:402
Sonic study

“Step-up” vs. “Top down”

**Step up**

Steroids

Steroids + AZA/MTX

IFX + AZA/MTX

**Top down**

IFX + AZA/MTX

AZA/MTX + IFX (on demand)

AZA/MTX + Steroids

**Primary outcome:** remission without steroids and without bowel resection at weeks 26 and 52

D’Haens et al. Lancet 2008;371;660
“Step-up” vs. “Top down” in CD

D’Haens et al. Lancet 2008;371;660
Conclusion

In patients who had been recently diagnosed with Crohn’s disease:

Top down approach was more effective than step up approach for:

- induction of remission
- maintenance of remission
- reduction of corticosteroid use

D’Haens et al Lancet 2008;371;660
However......

- In the conventional (step up) arm, no maintenance of AZA/MTX was given after the first course of corticosteroids.
- Chance of relapse over 1 yr is 75%.

- In the “top down” therapy, IFX was not given alone......AZA/MTX was given from the very beginning and during the entire study. AZA/MTX maintenance may play a major role.
### Effect of 6-MP on maintenance of remission

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>No. Pts</th>
<th>Medication</th>
<th>Duration</th>
<th>Control</th>
<th>Tx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candy(^{114})</td>
<td>1995</td>
<td>63</td>
<td>AZA (2.5)</td>
<td>12</td>
<td>58</td>
<td>93</td>
</tr>
<tr>
<td>Markowitz(^{168})</td>
<td>2000</td>
<td>55</td>
<td>MP (1.5)</td>
<td>18</td>
<td>9</td>
<td>47</td>
</tr>
<tr>
<td>Lémann(^{117}) (GETAID)</td>
<td>2005</td>
<td>83</td>
<td>AZA (1.7)</td>
<td>18</td>
<td>8</td>
<td>21</td>
</tr>
</tbody>
</table>

Markowitz J et al Gastroenterology 2000;119:895  
Candy S. Gut 1995;37:674  
Lemann M et al Gastroenterology, 2005, 128: 1812
Azathioprine vs. Placebo for maintenance of remission

Candy S. Gut 1995;37:674
ECCO Statement 6A

After the first presentation if remission has been achieved with systemic steroids, a thiopurine [EL1a, RG A] or methotrexate [EL1b, RG A] should be considered.

This policy was not practiced in the D’Haens study
“Step-up” vs. “Top down”

76% on AZA/MTX

Superiority of the “top down” therapy

Biological?

Immunosuppressive maintenance?
Sonic study

Low rate of response to azathioprine

AZA or 6-MP for induction of remission in CD (Cochrane)

- 8 randomized controlled trials
- 425 patients randomized
- Response rate for AZA/ 6-MP was 54%

The overall response rate was 113/209 (54%; 95% CI 47% to 61%) for treatment compared to 72/216 (33%; 95% CI 27% to 40%) for placebo.

Prefontaine E et al. Cochrane 2010
AZA or 6-MP for induction of remission in CD (Cochrane)

1.05 to 2.41). When remission or clinical improvement was measured before 17 weeks there was no statistically significant difference between antimetabolites and placebo (RR 1.08, 95% CI 0.83 to 1.40)

Chande N et al  Cochrane 2013
AZA or 6-MP for induction of remission in CD (Cochrane)

Azathioprine or 6-mercaptopurine patients evaluated at 17 weeks or later were significantly more likely to be in remission than those taking placebo (RR 1.59, 95% CI

Chande N et al  Cochrane 2013
Side effects of biologicals

- Infectious complications
- Malignancy
- Demyelinating disorders
- Autoimmunity
- Anaphylaxis
- Worsening of CHF
- Lymphoma/ heptosplenic T-cell lymphoma

Clark M et al. Gastroenterology 2007;133:312
Adverse effects related to IFX

- 6% serious adverse effects related to IFX
- 3.8% acute infusion reaction
- 2.8% serum sickness
- 0.6% Lupus
- 0.2% demyelization disorder
- 8.2% infection related to IFX
- 4.5% Serious infection; 0.4% death
- 1% mortality related to IFX

Colombel JF et al. Gastroenterology 2004;126:19
Anti TNF in pts older than 65 yrs

- 11% severe infections
- 3% neoplasms
- 10% died

Cottone M et al Clin Gastroenterol Hepatol; 2011:9:30
Top down therapy

Once anti-TNF given it is usually for a long time

It is not top down, it is top and stay!
Probability of infectious complication relative to No. IFX infusions

Colombel JF et al. Gastroenterology 2004;126:19
Most of CD patients have a benign course
Against “top down”

Half of the patients with Crohn’s disease never require corticosteroid therapy

Faubion WA et al Gastroenterology 2001
Munkholm P et al Gut 1994

Two thirds of CD patients’ life time is spent in remission

Silverstein MD et al Gastroenterology 1999

Lack of good biomarkers to identify high-risk patients
Escape of the effect of anti-TNF

- ACCENT 1: 57% initial response; < 20% of initial responders are in remission for 1 year

- ACCENT 2: 58% initial response; < 20% of initial responders are healed at 1 year
Mucosal healing and “no resection” in CD pts

- Mucosal healing at 1 yr: 44
  Resection: 6
- No healing at 1-yr: 62
  Resection: 18

1-yr mucosal healing is a predictor for resection

Froslie KF et al Gastroenterology 2007
Mucosal healing with azathioprine

- Complete colonic mucosal healing: 70%
- Complete ileal mucosal healing: 54%
- Histology:

D’Haens et al Gastrointest Endosc 1999;50:667
Two recent publications
Relative mortality in pts with IBD in Denmark (1982-2010)

<table>
<thead>
<tr>
<th></th>
<th>UC</th>
<th>CD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1982-1989</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>1990-1999</td>
<td>0.96 (0.90-1.02)</td>
<td>1.02 (0.93-1.12)</td>
</tr>
<tr>
<td>2000-2010</td>
<td>0.88 (0.82-0.95)</td>
<td>1.01 (0.91-1.13)</td>
</tr>
</tbody>
</table>
CD patients in remission -
Effect of AZA on operations
Maintenance of remission in AZA responders

Effect of AZA on intestinal surgery

Less intestinal surgery

Effect of AZA on peri-anal surgery

Less of perianal surgery

Accelerated step-up therapy for CD

- Budesonide (mild) ; prednisone (moderate)
- Sulphasalazine (colonic)
- 6-MP/ AZA
- Methotrexate
- Biologicals:
  - Infliximab
  - Adalimumab
- Others
ECCO Consensus 2010
Step up
Top down
Top down

Safety?
Cost
Mucosal healing and “no-colectomy” in UC pts

- Mucosal healing at 1 yr: 175
  - Colectomy: 3
- No healing at 1 yr: 176
  - Colectomy: 13

1-yr mucosal healing is a predictor for colectomy

Froslie KF et al Gastroenterology 2007
Long-term safety of infliximab

- Serious infection: 8.2% vs 4.2%  
  Sandborn WJ et al Gut 2004

- 6 fold increase in tuberculosis  
  Keane J et al NEJM 2001

- 1.7 fold increase in lymphoma  
  (combination IFX+AZA vs. AZA alone)  

- Hepatosplenic T cell lymphoma  
  (combination IFX + 6-MP)  
  Mackey ac et al J Pediatric 2007

- In rheumatoid arthritis:  
  - increase in malignancy- OR 3.3  
  Bongartz T et al JAMA 2006
Natural course of CD

Cosnes J. Inflm Bowel Dis 2002;8:244
“Top down” in Rheumatoid Arthritis

Early introduction of anti-TNF therapy results in modulation of the natural course with less progression of joint damage

Arthritis Rheum 2005;52:3381
Rev Med Brux 2001;22,174
Duration of response to IFX
Early CD (<2y) vs. Late CD (>2y)

Kugathasan S et al Am J Gastroenterol 2000;95:3189
“Top down” vs. “Step-up” in CD

• 129 CD pts with CDAI ≥ 200

• Steroid naïve

• Infliximab naïve

• Anti-metabolites naïve

D’Haens et al Lancet 2008; 371;660
AZA or 6-MP for induction of remission in CD (Cochrane)

Azathioprine or 6-mercaptopurine patients evaluated at 17 weeks or later were significantly more likely to be in remission than those taking placebo (RR 1.59, 95% CI)

Chande N et al  Cochrane 2013
Escape of anti-TNF effect

At one year:

• The ACCENT 1 study demonstrated that 28% of initial responders are in remission

• The ACCENT 2 study demonstrated that only one-fifth of all treated patients were healed

KammMA . Aliment Pharmacol Ther. 2006