“Top-down” therapy: Is the evidence strong enough?

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Short-term outcome in Crohn’s disease patients requiring systemic steroids

Disease activity

1-year outcome

Steroid dependency 22–23%
Surgery 35%

1 mo 1 year

Long-term outcome in Crohn’s disease. Stenosing and penetrating complications


Cosnes J, et al. Inflamm Bowel Dis 2002
Long-term outcome in Crohn’s disease. Requirements of intestinal resection

Cumulative probability of intestinal resection

Long-term outcome in Crohn’s disease.

Short-term outcome in patients with mild-to-moderate inflammatory activity

RCT comparing budesonide to placebo for maintenance of remission in CD patients with prior mild-to-moderate activity

Hanauer SB, et al. Aliment Pharmacol Ther 2005
Natural history of Crohn’s disease: Early control of disease and recurring flares

Observational study of 480 consecutive CD patients followed for 20 years (mean: 7.2 years) from disease diagnosis (1980–1999)

Tavarela-Veloso FT, et al. Inflamm Bowel Dis 2001
Prospective follow-up after a single IFX infusion of 15 pediatric patients with refractory CD.

Drug efficacy depends on disease duration

Drug efficacy depends on disease duration

**AZATHIOPRINE** as maintenance of steroid-induced remission

- early CD: 91%
- late CD: 42%
- steroid-dependent: 32%

**INFLIXIMAB** for induction of remission (3 infusions)

- early CD: 64%
- short-evolved CD: 59%
- late CD: 42%

**Median disease duration**

<table>
<thead>
<tr>
<th>early CD</th>
<th>late CD</th>
<th>steroid-dependent</th>
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<td>&lt;8 weeks</td>
<td>2.6 years</td>
<td>4 years</td>
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References:


Immune responses vary with time in CD

Cytokine production by T-cells from colonic mucosal biopsies in children with early CD (at diagnosis) or late CD (at least 5 years from diagnosis).

Treatment strategies and disease prognosis

**Good prognosis**
Treatment goal: symptom abatement
- Limited efficacy
- Minimal risk of AE

**Poor prognosis**
Treatment goals:
- Great efficacy
- Prevent disease complications
- Avoid admissions, surgeries, disability
- High risk of AE
Top-down strategies: Potential Pros and Cons

Pros

Longer remission periods
Less relapses
Less hospital admissions
Lower rates of intestinal resections

Cons

Overtreatment
Safety concerns: infections & malignancies
Economic concerns

CHANGING NATURAL HISTORY?

DO THEY REALLY CHANGE NATURAL HISTORY?
Early introduction of thiopurines

RCT comparing AZA vs PBO in new onset pediatric CD (<8 weeks). Initial course with 40mg PDN (n=55). 18-months follow-up.

Retrospective study. Pediatric new-onset CD cohort (The Netherlands). Clinical outcome after first remission with corticosteroids depending on the early introduction of AZA or not (n=58).


**Risk factors for surgery in pediatric CD patients**  
(multivariable Cox model)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Hazards ratio</th>
<th>95% CI</th>
<th>P value</th>
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<tr>
<td>B2 behaviour</td>
<td>2.54</td>
<td>1.58-4.01</td>
<td>&lt;0.01</td>
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<tr>
<td>Corticosteroids</td>
<td>2.98</td>
<td>1.64-5.41</td>
<td>&lt;0.01</td>
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<tr>
<td>AZATHIOPRINE</td>
<td>0.51</td>
<td>0.33-0.78</td>
<td>&lt;0.01</td>
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Conventional therapy vs ‘top-down’ in new onset CD

RCT comparing conventional therapy or “STEP-UP” (PDN→PDN → AZA →IFX) vs intensive therapy or “TOP-DOWN” (IFX+AZA →IFX →PDN) (n=133). All patients were naïve for immunomodulators and biologicals. 2-years follow-up.

Is it necessary to early introduce AZA in all CD patients?

... but still a great proportion relapse!!

Probability to remain in remission

“Top-down”

“Step-up”

P=0.031

Mucosal healing

SUTD endoscopic substudy after 2 years.

Proportion of patients with mucosal healing

- Top-down (IFX+AZA) n=26: 73%
- Step-up (PDN+/-AZA) n=23: 30%

Prognostic value of mucosal healing in new onset CD

Follow-up (4 years) of 42 CD patients included in the SUTD study.

Patients remaining in clinical remission after 4 years

P = 0.004

15/22

7/19

Baert F, et al. DDW 2008
What does it mean “top-down” therapy?

“Top-down” therapy:
early use of immunomodulators and biological agents.

Shergill & Terdiman. World J Gastroenterol 2008

“Top-down” therapy:
use of highly effective, but potentially more toxic, treatment strategies early in the course of a chronic disease, in order to prevent disease progression and complications.

How many ‘top-down’ strategies are there?

INDUCTION

STEROIDS (EN) + IMS

BIOLOGICALS + IMS

BIOLOGICALS + IMS

SURGERY + IMS

SURGERY + IMS

BIOLOGICALS

MAINTENANCE
‘top-down’, ‘middle-up’, or ‘accelerated step-up’?
Conclusions

✧ Conventional treatment strategies in CD are associated to a high rate of ‘complicated disease’ within the first 5-10 years from diagnosis.

✧ The earlier immunomodulators and/or biologicals are used, the better they work.

✧ To demonstrate that any drug changes CD’s natural history, long-term follow-up studies are needed, but maybe these could be replaced by mucosal healing assessment.
By now, only the early introduction of thiopurines has demonstrated to change natural history by reducing the risk of disease relapses and surgical requirements. Because useful predictors of disease outcomes are still lacking, early introduction of thiopurines may overtreat 10 to 30% of patients.

There are many potential ‘top-down’ strategies, but most of them have not been evaluated. Their evaluation and comparison in RCTs are warranted.
Lessons from post-operative recurrence: mucosal lesions and risk of clinical recurrence

How many ‘top-down’ strategies are there?

**BMC Surgery**

Study protocol

*Laparoscopic ileocolic resection versus infliximab treatment of distal ileitis in Crohn's disease: a randomized multicenter trial (LIR!C-trial)*

Ongoing RCT in patients with moderate to severe ileal CD that fail to respond to steroids or immunomodulators.

Impact of thiopurines on CD’s natural history

Retrospective study in a hospital cohort of 557 CD patients (CD diagnosis from 1978 to 2002). Assessment of therapeutic requirements and development of disease complications.

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<tr>
<td>Patients on IMS</td>
<td>0.04 (0.02-0.08)</td>
<td>0.14 (0.10-0.18)</td>
<td>0.27 (0.23-0.32)</td>
<td>0.45 (0.40-0.50)</td>
<td>0.63 (0.49-0.76)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Intestinal resection</td>
<td>0.36 (0.29-0.48)</td>
<td>0.30 (0.25-0.35)</td>
<td>0.32 (0.28-0.37)</td>
<td>0.31 (0.27-0.36)</td>
<td>0.36 (0.22-0.53)</td>
<td>0.528</td>
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<tr>
<td>Large intestinal resection</td>
<td>0.29 (0.23-0.35)</td>
<td>0.22 (0.18-0.27)</td>
<td>0.19 (0.16-0.23)</td>
<td>0.15 (0.11-0.19)</td>
<td>0.12 (0.05-0.28)</td>
<td>&lt;0.00001</td>
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Cumulative probability (95% CI)

Drug efficacy depends on timing

RCT in active CD comparing prednisolone 1 mg/kg/day (tapering dose to 12 weeks) associated to PLACEBO or AZATHIOPRINE 2.5 mg/kg/day for 15 mo (n=63). Patients stratified regarding ileal, colonic or ileocolonic disease. Median time since diagnosis at inclusion: AZA 2.6 years (0.1-19), PBO 3.7 years (0.1-18.7)

RCT comparing scheduled IFX infusions or episodic (on demand) IFX in active CD (ACCENT-1 trial).
Median disease duration at inclusion: 8 years (3.6-15).

Drug efficacy depends on timing

How many ‘top-down’ strategies are there?

- Surgery
- Biologicals
- Thiopurines / MTX
- Prednisone / Budesonide
- 5-ASA
- Antibiotics
efficacy in inducing mucosal healing

Mucosal healing after INDUCTION therapies

- **STEROIDS** (week 7) n=70
  - Landi B. Gastro 1992
- **ENTERAL NUTRITION** (week 8) n=25
  - Fell JME. APT 2000
- **INFLIXIMAB** (3 infusions) (week 10)
  - Rutgeerts P. GIE 2006
efficacy in maintaining (and inducing?) mucosal healing

Mucosal healing during MAINTENANCE therapies

1 Rutgeerts P, et al. ACCENT-1 substudy, 1 year (n=26). Gastrointest Endosc 2006
2 D’Haens G, et al. 2 years (n=20). Gastrointest Endosc 1999
Follow-up (4 years) of 42 CD patients included in the SUTD study.

**Patients remaining in clinical remission after 4 years**

- 15/22 with mucosal healing at 2 years
- 7/19 with endoscopic activity at 2 years

**P = 0.004**

Baert F, et al. DDW 2008