Top Down vs. Step Up Therapy
Biologics in IBD:
Treatment Algorithms

Stephen B. Hanauer, M.D.
University of Chicago
Treatment Goals c.2008

- Induce and maintain response/remission
- Prevent complications
  - Disease Related
  - Therapy Related
- Improve quality of life
- Limit surgery?
Conventional approach to Induction Therapy: step-up

- Clinical approach to use “mildest” form of drug therapy to treat patients first
- Move to next step in non-responders
Step-up management approach

Advantages

• Patients attain remission with less toxic therapies
• Potentially more toxic therapies reserved for more severe or refractory disease
• Minimizes risk of adverse events
• Cost sparing (short-term?)

Disadvantages

• Patients have to “earn” most effective treatments
• Decrease in quality-of-life before patients obtain optimal therapy
• Likelihood of surgery is high
• Disease is not modified
IBDs are chronic, life-long

We cannot just look at the short-term induction therapy
Long-Term Therapy for IBD is Sequential

Induction → Maintenance
Impact of Therapy will Depend on Degree of Structural Damage & Velocity of Progression

Impact of Therapy will Depend on Degree of Structural Damage & Velocity of Progression

Cosnes et al. Inflamm Bowel Dis 2002; 8: 244
Efficacy of AZA as Crohn’s Disease Maintenance Therapy After Steroids in Adults*


*Remission induced by prednisolone tapered over 12 wk
Inclusion: Patients were not steroid dependent
Efficacy of 6-MP as Crohn’s Disease Maintenance Therapy After Steroids in Steroid-naïve Children


At baseline, patients received prednisone plus either 6-MP or placebo. Steroids were tapered after induction of remission.
Three classes of anti-TNF: Fusion protein, antibodies and PEGylated Fab' fragment

- **Etanercept**
  - Human recombinant receptor/Fc fusion protein
  - Receptor
  - IgG1 Fc

- **Infliximab**
  - Chimeric
  - Fab
  - IgG1 Fc

- **Adalimumab**
  - Human
  - Monoclonal antibody

- **Certolizumab pegol**
  - PEGylated humanized Fab' fragment
  - 2 × 20 kDa PEG

Courtesy of Stephen B. Hanauer, M.D.
Clinical Trials with Anti-TNF Biologics in Refractory Crohn’s disease

- Targan/Infliximab
- Classic I/Adalimumab
- ACCENT I/Infliximab
- CHARM/Adalimumab
- PRECiSE 2/Certolizumab
- CLASSIC II/Adalimumab
- PRECiSE 1/Certolizumab
Comparing ACCENT I, CHARM, and PRECiSE 2 Results

ACCENT I* (infliximab)

- Week 2 Response: 58.5%
- Week 30 Remission: 39.0%
- Overall Remission Week 30: 22.8%

CHARM** (adalimumab)

- Week 4 Response: 60%
- Week 26 Remission: 40%
- Overall Remission Week 26: 24%

PRECiSE 2 (certolizumab pegol)

- Week 6 Response: 64.1%
- Week 26 Remission: 47.9%
- Overall Remission Week 26: 30.7%

*5 mg/kg dose.
**Maintenance trial with 80/40 mg induction dosing. Randomized responders = CR-70 at week 4. Week 26 remission among randomized responders on 40 mg every other week dosing.
Impact of Disease Duration
Clinical Remission at Weeks 26 by Disease Duration in adalimumumab CHARM study


*p=0.002, **p<0.001, †p=0.014, ‡p=0.001 all vs placebo
Week 26 Remission with certolizumab by Duration Of Crohn’s Disease In PRECiSE 2

- Certolizumab Remission
- Placebo Remission

<table>
<thead>
<tr>
<th>Duration</th>
<th>Certolizumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 Year</td>
<td>68%</td>
<td>37%</td>
</tr>
<tr>
<td>1 - 2 Years</td>
<td>55%</td>
<td>36%</td>
</tr>
<tr>
<td>2 - 5 Years</td>
<td>47%</td>
<td>29%</td>
</tr>
<tr>
<td>&gt; 5 Years</td>
<td>44%</td>
<td>24%</td>
</tr>
</tbody>
</table>
Impact of Concomitant Immunomodulators
ACCENT I: Comparable clinical outcomes with or without immunomodulators

Lichtenstein et al, Gastroenterology 2007; 132: A-146 (No. 982)
CHARM: Effect of concomitant adalimumab and immunosuppressive therapy on remission at week 26 and 56

Colombel et al, Gastroenterology 2007; 132: 52
Continuous vs interrupted use of immunomodulators in the long-term efficacy of infliximab (IFX): The IMID Trial

- 80 patients randomized to continue (+CON, n=40) or to interrupt (++DIS, n=40) immunomodulators (azathioprine or methotrexate) 6 months after the start of infliximab (5 mg/kg IV)

No need for early ‘rescue’ IFX: primary endpoint

Median IFX levels, Week 8 to Week 104 combined

Log Rank (Cox): 0.735; Breslow: 0.906

p<0.005

Van Asche et al, Gastroenterology 2007; 132: A-103 (No. 734)
### Recent Anti-TNF Biologic Trials

#### Step-up/Top-down (Steroid-naïve)
- **COMMITT** (Steroid-induced, IS naïve)
- **SONIC** (Steroid-refractory, IS naïve)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment Paths</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMMITT</td>
<td>Steroids $\rightarrow$ Steroids $\rightarrow$ IS $\rightarrow$ Infliximab $\rightarrow$ Infliximab $\rightarrow$ Infliximab + MTX $\rightarrow$ Infliximab + AZA</td>
</tr>
<tr>
<td>SONIC</td>
<td>Steroids $\rightarrow$ Steroids $\rightarrow$ Steroids $\rightarrow$ Infliximab + AZA $\rightarrow$ AZA</td>
</tr>
</tbody>
</table>
Early Aggressive Biologic Therapy vs Conventional Management of Crohn’s Disease

Newly diagnosed, antimetabolite, anti-TNF, or steroid-naïve CD patients (n=133)

- Conventional therapy (n=66)
  - Steroids

- Early aggressive (n=67)
  - + IFX
  - + AZA
  - IFX (0,2,6 weeks) + AZA
  - + (episodic) IFX

Step-Up vs. Top-Down: Results

CDAI < 150 & No Steroids

- 60% of Patients at 6 Months for Step-Up vs. 41% for Top-Down: \( P = 0.03 \)
- 61% of Patients at 12 Months for Step-Up vs. 50% for Top-Down: \( P = 0.19 \)

Steroid Use

- 0% of Patients at 6 Months for Step-Up vs. 31% for Top-Down: \( P < 0.001 \)
- 0% of Patients at 12 Months for Step-Up vs. 17% for Top-Down: \( P < 0.001 \)

Treatment Success* From Week 14 Through 2 Years

- 29% for Top-Down vs. 5% for Step-Up: \( P < 0.001 \)

*Remission (CDAI < 150), discontinuation of steroids and infliximab, and no resection.

Step Up vs. Top Down: Complete Endoscopic Remission at 2 Years


- Early aggressive therapy (n=26): 73%
- Conventional therapy (n=23): 30%

**p=0.003
Patients with active CD on corticosteroids within last 6 weeks

1:1 randomization to
- IFX + PBO (n=63)
- IFX + MTX (n=63)

Steroids withdrawn by Week 14 per protocol

IFX at 0, 2, and 6 weeks then maintenance q8W

Primary analysis: time to treatment failure
- CDAI <150, no prednisone by Week 14 and maintained to Week 50
- Relapse: CDAI increase of 70 points

• No difference in ITT analysis, duration of disease <2 years, by CDAI score

• No difference in infectious AEs (58.7% MTX vs 61.9% PBO)

SONIC

Induction + maintenance of
steroid-free remission,
mucosal healing,

IFX monotherapy vs
IFX+AZA combination vs
AZA monotherapy

in moderate-to-severe CD in patients with no
prior exposure to biologic agents and
immunosuppressants

Cosnes et al. Inflamm Bowel Dis 2002; 8: 244
Clinical remission without corticosteroids at week 26

Primary endpoint

<table>
<thead>
<tr>
<th>Proportion of Patients (%)</th>
<th>AZA + placebo</th>
<th>IFX + placebo</th>
<th>IFX+ AZA</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>52/170</td>
<td>75/169</td>
<td>96/169</td>
</tr>
<tr>
<td>100</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

p<0.001  p=0.009  p=0.022

Sandborn et al., ACG 2008 annual meeting, abstract #29
Mucosal healing at week 26

Secondary endpoint

Proportion of Patients (%)

- AZA + placebo: 18/109
- IFX + placebo: 28/93
- IFX + AZA: 47/107

p<0.001
p=0.023
p=0.055

Sandborn et al., ACG 2008 annual meeting, abstract #29
COMMITT vs. SONIC

**COMMITT**
- Steroid-induced patients
- IS Naïve
- Steroid-Induced
- Forced steroid-taper by week 14

**SONIC**
- 40% Steroid-dependent (refractory CDAI>250)
- IS Naïve
- Ad lib steroids to week 14 (↑↔↓) then taper

Cosnes et al. Inflamm Bowel Dis 2002; 8: 244
Yin & Yang of Concomitant Immunomodulators

- All biologics are immunogenic
- Antibodies (at least to infliximab)
  - Associated with acute/delayed infusion reactions
  - Shorter duration of response (with episodic therapy)
- Immunomodulators reduce immunogenicity across all trials

Yet...
- No difference in short- or long-term responses to induction + maintenance therapy in refractory CD
  - ACCENT, CHARM, PREcISe
- No benefit with steroid-induction (COMMIT)
- Positive Benefit in steroid-dependent (SONIC)
- Increase long-term toxicity
  - Serious infections
  - Risk of neoplasia
Anti-TNF-α Risks

• Immunogenicity (all biologics)
• Infliximab specific
  – Infusion reactions
• Class effect
  – Drug-induced lupus
  – Injection site reactions (adalimumab, certolizumab pegol)
  – Non-Hodgkin’s lymphoma (including hepatosplenic T-cell lymphoma in children on infliximab + azathioprine)
  – Serious infections (~3%)
  – Opportunistic infections (including tuberculosis, histoplasmosis, coccidiomycosis)
  – Demyelination
When to Introduce Biologics?

The “Tipping Point” may be Corticosteroids?
Challenges of Induction → Maintenance 2009: Consider the Population

Steroid-Naïve

Steroid-Induction →
Thiopurine/MTX Maintenance (Markowitz)

Anti-TNF Induction →
Thiopurine/MTX Maintenance (Step-up/Top-Down)
Challenges of Induction → Maintenance 2009:
Consider the Population

Steroid-Dependent
Thiopurine/MTX Maintenance
(Candy, Markowitz, Feagan)

Failure
Biologic (ACCENT, CHARM, PREcISE)
Challenges of Induction → Maintenance 2009: Consider the Population

Steroid-Refractory
Immunosuppressive naïve

Anti-TNF + AZA induction & Maintenance (SONIC)

Fail
Assess Inflammation, Immunogenicity
Switch Anti-TNF or Natlizumab

Steroid-Refractory
Despite Immunosuppressive

Anti-TNF induction & Maintenance

Stop Immunosuppressive
### Current and Future Therapeutic Paradigms

<table>
<thead>
<tr>
<th>Current</th>
<th>Future</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Bottom-up approach</td>
<td>• Early aggressive approach</td>
</tr>
<tr>
<td>• Conservative use of immunomodulators</td>
<td>• Earlier use of immunomodulators</td>
</tr>
<tr>
<td>• Goals</td>
<td>• Additional goals</td>
</tr>
<tr>
<td>– Induce remission</td>
<td>– Disease modification</td>
</tr>
<tr>
<td>– Maintain remission</td>
<td>– Mucosal healing</td>
</tr>
<tr>
<td>– Prevent complications</td>
<td>– Pharmacoeconomics</td>
</tr>
<tr>
<td>– Optimize surgical outcomes</td>
<td>• Disease prevention!</td>
</tr>
</tbody>
</table>