Biologics: The Future of IBD Therapy

Stephen B. Hanauer, M.D.
University of Chicago
Conflicts of Interest

- Abbott
- Centocor
- Ferring
- P&G
- Prometheus
- Schering-Plough
- Shire
- UCB

With Thanks to Falk Foundation & CMS
Thoughts on IBD Therapy from West → East
Interleukin 23 (IL23) orchestrates intestinal inflammation via multiple pathways

Whereas Conventional small molecules: 5-ASA, Steroids, Thiopurines and Methotrexate are Pluripotent & Non-Specific

Biologics Provide Targeted Therapy
1. Antigen Processing & Presentation, Activation of Macrophages
- Antibiotics
- Probiotics

2. Antigen Recognition & Activation of CD4+ T cells
- Anti-CD3 Antibodies
- ?MTX

3. Production of Proinflammatory Cytokines
- Anti-TNF Antibodies
- Anti-IL12/23 Antibodies
- Anti-IL 17 Antibodies
- Anti-IL 16R
- Anti-NFKB or STAT signalling

4. Inflammation and Injury
- Apheresis
- ?Nicotine

5. Recruitment, Migration and Adhesion
- Anti-α4 & Anti-α4β7 integrin antibody
- Antisense oligonucleotide to ICAM-1
- Chemokine inhibitors

6. Repair and Restitution
- IL-11
- Growth Factors

Biologic Treatment Targets
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

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

**Advantages**

- Patients attain remission with less toxic therapies
- Reserves more Potent & more Toxic therapies 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
Maintenance Therapy is Dictated by Induction Therapy

\[ \text{Induction \rightarrow Maintenance} \]

Aminosalicylate $\rightarrow$ Aminosalicylate
Maintenance Therapy is Dictated by Induction Therapy

Induction
Corticosteroid

Maintenance
Aminosalicylate (UC)
Thiopurine
Methotrexate (CD)
Maintenance Therapy is Dictated by Induction Therapy

Induction: Anti-TNF

Maintenance: Thiopurine (Steroid-Naïve) Anti-TNF (Steroid-Refractory)
Maintenance Therapy is Dictated by Induction Therapy

- **Induction**
  - Natalizumab

- **Maintenance**
  - Natalizumab
Construct of anti-TNF-α biologic agents for IBD

- **Chimeric monoclonal antibody**
  - Infliximab

- **Human monoclonal antibody**
  - Adalimumab

- **Humanized Fab’ fragment**
  - Certolizumab pegol
<table>
<thead>
<tr>
<th>Agent</th>
<th>Mode of action</th>
<th>Route</th>
<th>Half-life (days)</th>
<th>Interval between injections (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TNF neutralization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infliximab</td>
<td>+</td>
<td>ADCC, CF</td>
<td>IV</td>
<td>10</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>+</td>
<td>ADCC, CF</td>
<td>SC</td>
<td>12–14</td>
</tr>
<tr>
<td>Certolizumab pegol</td>
<td>+*</td>
<td>No</td>
<td>SC</td>
<td>14</td>
</tr>
</tbody>
</table>

- **In vitro data**
- *Neutralization of soluble anti-TNF-α: certolizumab pegol > adalimumab > infliximab*

*Gramlick et al, Gastroenterology 2006; 130: A-697*
Biological Agents Targeting TNFα are the Most Effective Agent, to date, to Treat IBD
Improvement in Clinical Response With Infliximab*

* Patients NOT RESPONDING to Conventional Agents

Fistula Healing With Infliximab*

* Patients NOT RESPONDING to Conventional Agents

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>13% (4/31)</td>
</tr>
<tr>
<td>5 mg/kg</td>
<td>55% (17/31)</td>
</tr>
<tr>
<td>10 mg/kg</td>
<td>38% (12/32)</td>
</tr>
</tbody>
</table>

* p < 0.001.
† p < 0.041.

Complete response defined as all fistulas closed for 2 consecutive visits (at least 1 month).
Accent I:
Infliximab Maintenance Prolongs Response Through Week 54

*Patients NOT RESPONDING to Conventional Agents

Week 2 Responders

- 10 mg/kg q 8 wks
  - > 54 weeks
  - $P < 0.001$

- 5 mg/kg q 8 wks
  - 38 weeks
  - $P = 0.028$

- Single dose
  - 19 weeks
  - $P = 0.002$

ACT 1 and ACT 2: Clinical Remission with Infliximab in UC*

Clinical remission defined as Mayo score of ≤2 points, with no individual subscore >1.

Patients with baseline medication were continued on stable doses.


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*Placebo infusions*  
5 mg/kg infliximab  
10 mg/kg infliximab

---

*Clinical remission defined as Mayo score of ≤2 points, with no individual subscore >1.*
ACT 1 and ACT 2: Mucosal Healing in UC

**Mucosal healing** defined as endoscopy subscore of 0 or 1.

- Patients with baseline medication were continued on stable doses.

**Proportion of Patients (%)**

- **ACT 1**
  - Week 8: Placebo infusions (34%), 5 mg/kg infliximab (62%), 10 mg/kg infliximab (59%)
  - Week 30: Placebo infusions (25%), 5 mg/kg infliximab (50%), 10 mg/kg infliximab (49%)

- **ACT 2**
  - Week 8: Placebo infusions (31%), 5 mg/kg infliximab (60%), 10 mg/kg infliximab (62%)
  - Week 30: Placebo infusions (30%), 5 mg/kg infliximab (46%), 10 mg/kg infliximab (57%)

Infliximab: Endoscopic Healing in Crohn’s Disease

Patterns Demonstrating Endoscopic Healing (%)

Week 10
- Single dose: 0/17 (31%)
- Combined dose group (5 mg/kg & 10 mg/kg infliximab maintenance): 1/14 (7%)

Week 54
- 5 mg/kg infliximab maintenance: 5/11 (46%)
- 10 mg/kg infliximab maintenance: 8/15 (53%)

*Among Week-2 responders (n=66)

Infliximab: Endoscopic Healing and Reduced Hospitalizations and Surgeries

<table>
<thead>
<tr>
<th>Patients with no healing (n=74)</th>
<th>Patients with healing at 1 visit (10 or 54 wk) (n=16)</th>
<th>Patients with healing at both visits (10 and 54 wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization</td>
<td>Hospitalization</td>
<td>Hospitalization</td>
</tr>
<tr>
<td>Surgery</td>
<td>Surgery</td>
<td>Surgery</td>
</tr>
</tbody>
</table>

- Hospitalization: 46% (34*)
- Surgery: 0%

*Number per 100 patients

Once starting on Biologic Therapy Maintenance Therapy is Superior to Episodic Therapy

Impact of infusion regimens

- **Conclusion**: Scheduled dosing is superior to episodic dosing regarding hospitalization, surgery and disability.

Williams J et al. DDW 2005, W1076
Anti-TNF-α Risks

• Immunogenicity (all biologics)
  – Increased with episodic therapy
  – Infusion reactions (infliximab)
  – Injection site reactions (adalimumab, certolizumab pegol)
• Serious infections (~3%)
  – Opportunistic infections (including tuberculosis, histoplasmosis, coccidiomycosis)
• Lymphoma
• Demyelination
• Drug-induced lupus
## Opportunistic infections and anti-TNF therapies:

Ex: from Risk Factors for Opportunistic Infections in IBD

<table>
<thead>
<tr>
<th>Medication</th>
<th>Odds Ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any medication (5-ASA, AZA/6MP, Steroids, MTX, Infliximab)</td>
<td>3.50 (1.98-6.08)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>5-ASA</td>
<td>0.98 (0.61-1.56)</td>
<td>0.94</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>3.35 (1.82-6.16)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AZA/6MP</td>
<td>3.07 (1.72-5.48)</td>
<td>0.0001</td>
</tr>
<tr>
<td>MTX</td>
<td>4.00 (0.36-4.11)</td>
<td>0.26</td>
</tr>
<tr>
<td>Infliximab</td>
<td>4.43 (1.15-17.09)</td>
<td>0.03</td>
</tr>
<tr>
<td>One medication</td>
<td>2.65 (1.45-4.82)</td>
<td>0.0014</td>
</tr>
<tr>
<td>Two medications</td>
<td>9.66 (3.31-28.19)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

If Biologics are Most Effective Therapy to Date…. Why not use First

• Cost?
• Side effects?
The Main Reason

Most patients don’t need them
Hospitalization Accounts for >50% of Health Care Costs in CD*

*Data from patients with a CD-related medical claim (10/94-09/95) included in a 1994 integrated claims database.

80/20 Rule

- 80% of the Costs are Accounted for by 20% of Patients….
- And that 20% have the most severe and/or complex disease
Is Biological Therapy a “Means to an End”

- Monoclonal Antibodies originally developed as a “Proof of Concept” for eventual development of small molecules
- Financial success of Biologicals has created pharmaceutical “Ends”
- Future small molecules may supplant biologics and further improve health care economics
So let’s consider Asia & Developing Countries where IBD is Uncommon
Ulcerative Colitis: Severity at Presentation
Less than 10% Present with Severe Disease

Hendriksen C, Kreiner S, Binder
In “Developing Countries” Prevalence of Severe Disease is Low

- Severe Activity (9%)
- Moderate Activity 71%
- Mild Activity 20%
Evolution of Crohn’s Disease Behavior over 20 years

Timeline for Complicated Disease in Asia?
20+ years?

Cumulative Probability (%)

Patients at risk:

N = 2002 552 229 95 37

Inflammatory
Penetrating
Stricturing

Cosnes J et al. Inflamm Bowel Dis. 2002;8:244.
Unless the Incidence of IBD Greatly Accelerates in Asia

Over Next Decades Prevalence of Severe/Complex IBD Should Remain Relatively Low
Impact of Disease Duration and Prior Therapies Applies to Short & Long-term Response with Biologics
Impact of Therapy will Depend on Degree of Structural Damage & Velocity of Progression

Cumulative Probability (%)

Patients at risk:
N = 2002

Months
0 12 24 36 48 60 72 84 96 108 120 132 144 156 168 180 192 204 216 228 240

Inflammatory
Stricturing
Penetrating

High Potential
Low Potential

Cosnes J et al. Inflamm Bowel Dis. 2002;8:244.
Should Biologics be used Earlier in IBD?

- Anti-TNF is more efficacious than conventional therapies
- Anti-TNFs are safer than conventional therapies (Corticosteroids)
- May be more cost-effective (over time) than conventional therapies

- Conventional Therapies Induce/Maintain Remissions in majority of patients
- Majority of patients do not need cost/toxicity risks of biologics
- Long-term safety experience in children & pregnancy
- Can we transition back to conventional immune modulators as in RA?
When to Introduce Biologics?

The “Tipping Point” may be Corticosteroids?

At Least in the West
Can therapy alter the natural history of Crohn’s disease?

**Disease complications**

- Induce and maintain gastrointestinal healing
- Prevent need for steroids
- Prevent strictures and penetrating complications
- Prevent extra-intestinal complications
- Decrease hospitalization / surgery
- Decrease long-term cost of care

**Natural course**

**Years**
Comparison of Goals

**Current**
- Symptom control (induce and maintain remission)
- Improve quality of life
- Minimize drug toxicity
- Minimize disease complications
- Optimize surgical outcomes

**Future**
- Mucosal healing
- Disease modification
- *Predictive Biomarkers*
- *Molecular/Genetic markers* predicting course & therapeutic response
- Find the cause…
- Eliminate or tolerize to Environmental factors
Current Therapeutic Paradigms Where Disease is Mild

• Conventional, step-up approach according to disease severity/complexity
• Conservative use of immunomodulators & Biologics
• Goals
  – Induce remission
  – Maintain remission
  – Prevent complications
  – Optimize surgical outcomes
Future Therapeutic Paradigms as Disease Becomes more Prevalent/Severe/Complex

• Early aggressive approach
• Earlier use of immunomodulators
• Additional goals
  – Disease modification
  – Mucosal healing
  – Pharmacoeconomics

• Disease prevention!... Worldwide
So, What’s Happening in Asia to Increase Incidence of IBD?
And...What are the Results?
Fast Food Arrives in Africa
WILL IT BE THE MAD COW BEEF, THE HORMONE CHICKEN, OR THE MERCURY FISH?
The Goal of Disease Prevention?