“Biologic Therapy in Inflammatory Bowel Disease”

Raymond Cross, MD, MS
Associate Professor of Medicine
Director, IBD Program
University of Maryland School of Medicine Chief, Gastroenterology Section
Baltimore VAMHCS

Update in Inflammatory Bowel Disease

11/19/10
Disclosures

- Research Support: Abbott, Centocor, and Prometheus
- Educational Support: Abbott, P&G, and Shire
- Consulting: Abbott
Biologic Questions in Clinical Practice

- Which patient should be started on biologic therapy?
- When should a patient be started on biologic therapy?
- Which biologic should I use?
- How do you optimize biologics over the long term?
- What do you do when a patient is losing response to therapy?
- Which patients should be treated with concurrent immune suppressants?
- How do you counsel patients on the risks of therapy?
<table>
<thead>
<tr>
<th>Molecule Type</th>
<th>Infliximab</th>
<th>Adalimumab</th>
<th>Certolizumab pegol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecule Type</td>
<td>Chimeric monoclonal antibody</td>
<td>Fully human monoclonal antibody</td>
<td>Humanized PEGylated Fab fragment</td>
</tr>
<tr>
<td>Fixes complement/ cell lysis?</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Mode</td>
<td>IV</td>
<td>SC</td>
<td>SC</td>
</tr>
<tr>
<td>Frequency</td>
<td>Every 8 weeks</td>
<td>Every 1-2 weeks</td>
<td>Every 4 weeks</td>
</tr>
</tbody>
</table>
## Dosing with Biologics

<table>
<thead>
<tr>
<th></th>
<th>Starting Dose</th>
<th>Escalating Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infliximab</strong></td>
<td>5 mg/kg IV – 3-dose induction, q 8 weeks</td>
<td>10 mg/kg IV q 8 weeks or more often</td>
</tr>
<tr>
<td><strong>Adalimumab</strong></td>
<td>160 mg SC Week 0; 80 mg Week 2; 40 mg q 2 weeks</td>
<td>40 mg subQ weekly</td>
</tr>
<tr>
<td><strong>Certolizumab</strong></td>
<td>400 mg SC Weeks 0, 2, 4 then q 4</td>
<td>400 mg?</td>
</tr>
</tbody>
</table>
Summary of Induction Studies of Anti-TNF Therapy in CD

Targan et al, NEJM 1997
Hanauer et al, Gastro 2006

*Results represent difference between active drug and placebo at 4 weeks
Summary of Maintenance Studies of Anti-TNF Therapy in CD

Colombel et al. Gastro 2007
Schreiber et al. NEJM 2007

*Results represent difference between active drug and placebo at ~ 6 and 12 months
Response to Medical Therapy is Poor in Patients with Complicated Crohn’s Disease

64% of patients required surgery

Infliximab for Moderate to Severe Refractory UC

Clinical Response at Week 8

Clinical Remission at Week 8

ADA in Patients with Moderate to Severe UC Failing Steroids and IS

Reinisch et al, ACG 2010

*p=<0.05 ADA 160/80 compared to placebo
Fistula Response at Week 54

ACCENT II

- Fistula response: 23% (Placebo) vs. 46% (5 mg/kg infliximab) with p = 0.001
- Complete response: 19% (Placebo) vs. 36% (5 mg/kg infliximab) with p = 0.009

Patients in Response (%)
Complete Fistula Closure at 56 Weeks

Percent of patients who had complete closure at the last two visits of all fistulas that were draining at baseline

- For this analysis, both HUMIRA 40 mg eow and ew groups were included, regardless of response to HUMIRA at Week 4

PRECiSE 2: Fistula Healing with CTZ

* Absence of drainage post baseline at 2 consecutive visits

Schreiber et al. NEJM 2007
Management of Patients Losing Response to Anti-TNF Therapy

- Dose escalation required in ~30% of patients treated with anti-TNF
  - IFX
    - Increase dose
    - Increase frequency of infusions
    - Use of trough and HACA levels to guide therapy?
  - ADA
    - Increase frequency of injections
    - Mini-reinduction?
  - CTZ
    - Early/extra dose of drug
Clinical utility of measuring IFX and HACA levels in patients with IBD

Clinical outcomes in patients with detectable HACA (n=35)

Complete / partial response (%)

- Anti-TNF changed (11/12)
  - Complete / partial response: 92%
  - P < 0.004

- Infliximab increased (1/6)
  - Complete / partial response: 17%

Clinical outcomes in patients with sub-therapeutic concentrations (n=69)

Complete / partial response (%)

- Anti-TNF changed (2/6)
  - Complete / partial response: 33%

- Infliximab increased (25/29)
  - Complete / partial response: 86%

Results changed management in 73% of cases

428 patients responded to OL CTZ at week 6 in PRECiSE 2

- 124 patients relapsed
  - n=49 on CTZ maintenance
  - n=75 on placebo maintenance

CTZ 400 mg subcut given at week 0, 2, 4 
(one extra dose given)

- 63 and 65% of patients responded
- 55 and 59% of responders maintained response at one year

GAIN: Efficacy Outcomes at Week 4

% of Patients

Remission
Response CR-70
Response CR-100

PBO 160/80 mg

7 21 38
12/166 34/159
56/166 82/159
41/166 61/159

*P<0.001, †P<0.01, both vs. placebo.

WELCOME: Efficacy results in DB maintenance period

OL Induction Phase

Clinical Response and Remission at Wk 26

Primary Endpoint: CR100 at Wk 6

α4 integrins are key intestinal adhesion molecules

Podolsky et al. *JCI* 1993;92:372-80
Hesterberg PE et al. *Gastroenterology* 1996;111:1373-80
ENACT-1: Response

- Placebo (n=181)
- Natalizumab (n=724)

Patients (%)

Week 2: 33%
Week 4: 45%
Week 6: 53%
Week 8: 50%
Week 10: 49%
Week 12: 51%

P = 0.009

ENACT-1: Response at Week 10
Subgroup Analysis


*P<0.05
ENACT-2: Sustained Clinical Remission at Every Assessment

PRECiSE 2: Clinical response at Week 26 by immunosuppressant use (ITT)

Clinical response: ≥100-point reduction in CDAI

* *p<0.001

Results: IMID

No need for early ‘rescue’ IFX: primary endpoint

Log Rank (Cox): 0.735; Breslow: 0.906

Median IFX levels, Week 8 to Week 104 combined

IFX trough levels (μg)

p<0.005

Van Assche G et al. Gastroenterology 2008
# Probability of Surgery for Crohn’s Disease

<table>
<thead>
<tr>
<th>Years After Diagnosis</th>
<th>Patients (%)</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 Surgery</td>
<td>2 Surgeries</td>
<td>≥ 3 Surgeries</td>
<td>No Surgery</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>37</td>
<td>7</td>
<td>5</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>39</td>
<td>11</td>
<td>12</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>moderate</td>
<td>34</td>
<td>14</td>
<td>22</td>
<td>mild</td>
</tr>
</tbody>
</table>

Weighing the Value of Early Biologic Therapy

**Benefits**

- Maintenance of remission
- Improved function and QOL
- Early promotion of mucosal healing to prevent complications

**Disadvantages**

- Side effects
- Cost
- Majority of patients may not require more potent treatments initially

**PRECiSE 2: Week 26 Clinical Response or Remission by Duration of Crohn’s Disease**

<table>
<thead>
<tr>
<th>Duration of Crohn’s Disease (years)</th>
<th>Response Patients (%)</th>
<th>Remission Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1</td>
<td>Certolizumab: 37</td>
<td>Placebo: 37</td>
</tr>
<tr>
<td>1 to &lt; 2</td>
<td>Certolizumab: 50</td>
<td>Placebo: 50</td>
</tr>
<tr>
<td>2 to &lt; 5</td>
<td>Certolizumab: 36</td>
<td>Placebo: 36</td>
</tr>
<tr>
<td>≥ 5</td>
<td>Certolizumab: 33</td>
<td>Placebo: 33</td>
</tr>
</tbody>
</table>

*< 1 1 to < 2 2 to < 5 ≥ 5*  

*< 1 1 to < 2 2 to < 5 ≥ 5*  

*P < 0.01; †P < 0.05; ‡P < 0.001 vs placebo.  
The ideal management of CD: Top down versus step up strategies

- Open-label trial, 26 centers in Belgium, Holland, Germany
- Active CD of less than 4 y duration naïve to immunomodulators and biologics
- Co-primary endpoint at 6 and 12 months, follow up 24 months:
  - REMISSION – OFF STEROIDS – NO RESESECTION

Newly diagnosed Crohn’s disease (n=129)

Step up (n=64)
- Steroids
- + AZA
- + MTX
- + IFX

Top down (n=65)
- IFX (0/2/6) + AZA
- IFX + AZA
- + (episodic) IFX
- Steroids

Top down versus step up: Results

CDAI <150 AND no steroids AND no surgery

Proportion of pts on immunosuppressants

*D p<0.01
**D p<0.05

# Top-down versus step-up: Endoscopic results

<table>
<thead>
<tr>
<th></th>
<th>Top-down (n=65)</th>
<th>Step-up (n=64)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crohn’s lesions after 2 years</td>
<td>Baseline 2 years</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5.6 ± 2.7</td>
<td>5.3 ± 2.4</td>
</tr>
<tr>
<td></td>
<td>0.7 ± 1.5 Change</td>
<td>3.1 ± 2.9 Change</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.0001</td>
<td>p=0.003</td>
</tr>
<tr>
<td>Endoscopic subset (n=49)</td>
<td>73%</td>
<td>30%*</td>
</tr>
<tr>
<td>*p=0.003</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SONIC
Corticosteroid-Free Clinical Remission at Week 26

Primary Endpoint

Proportion of Patients (%)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Proportion</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZA + placebo</td>
<td>30.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IFX + placebo</td>
<td>44.4</td>
<td>0.009</td>
</tr>
<tr>
<td>IFX + AZA</td>
<td>56.8</td>
<td>0.022</td>
</tr>
</tbody>
</table>

52/170 75/169 96/169

Columbel et al. NEJM 2010
Mucosal Healing at Week 26

SONIC

Columbel et. al. NEJM 2010
Endoscopic Recurrence Reduced in IFX Treated Patients

Endoscopic Recurrence defined as endoscopic scores of i2, i3, or i4.
One Year Clinical Recurrence Reduced in IFX Treated Patients

Clinical recurrence defined by 54 week CDAI > 200.
### Safety of infliximab and other Crohn’s disease therapies – TREAT Registry Data

#### Serious infections (Multivariate)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current use of IFX</td>
<td>1.4</td>
<td>0.9–2.1</td>
</tr>
<tr>
<td>Current use of 6-MP/AZA/MTX</td>
<td>0.9</td>
<td>0.6–1.3</td>
</tr>
<tr>
<td>Current use of corticosteroids</td>
<td>2.0</td>
<td>1.4–2.9†</td>
</tr>
<tr>
<td>Current use of narcotic analgesics</td>
<td>2.7</td>
<td>1.9–4.0†</td>
</tr>
</tbody>
</table>

**†p<0.0001**

#### Mortality (Multivariate)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current use of IFX</td>
<td>1.1</td>
<td>0.6–1.8</td>
</tr>
<tr>
<td>Current use of 6-MP/AZA/MTX</td>
<td>0.8</td>
<td>0.5–1.2</td>
</tr>
<tr>
<td>Current use of corticosteroids</td>
<td>2.2</td>
<td>1.4–3.7*</td>
</tr>
<tr>
<td>Current use of narcotic analgesics</td>
<td>2.6</td>
<td>1.6–4.3**</td>
</tr>
</tbody>
</table>

* *p=0.001; **p<0.001

Risk factors for opportunistic infections in IBD: a case-control study (100 cases, 1983-2003)

<table>
<thead>
<tr>
<th>Odds Ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 medication</td>
<td>2.7 (1.5–4.8)</td>
</tr>
<tr>
<td>2 medications</td>
<td>9.7 (3.3–28.2)</td>
</tr>
<tr>
<td>3 medications</td>
<td>Infinite</td>
</tr>
</tbody>
</table>

Overall p<0.0001

Steroids alone        | 2.2 (1.1–4.8) | 0.037  |
6MP/AZA alone         | 2.5 (1.2–5.1) | 0.015  |
IFX alone             | 11.2 (0.8–153.3) | 0.07 |
6MP/AZA – steroids    | 15.7 (4.1–59.5) | <0.0001 |
6MP/AZA – IFX         | 1.6 (0.1–18.7) | 0.71   |
6MP/AZA – IFX – steroids | Infinite | 0.0003 |

## Meta Analysis of Lymphoma Rate Associated with Anti-TNF Agents

<table>
<thead>
<tr>
<th></th>
<th>NHL rate/10,000</th>
<th>IRR</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEER</td>
<td>1.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IM</td>
<td>3.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti TNF v SEER</td>
<td>6.1</td>
<td>3.23</td>
<td>1.5-6.9</td>
</tr>
<tr>
<td>Anti TNF v IM</td>
<td>6.1</td>
<td>1.7</td>
<td>0.5-7.1</td>
</tr>
</tbody>
</table>

Siegel et al, Clin Gastroenterol Hepatol 2009
HSTCL

- 200 cases in medical literature
  - 9 cases associated with IS alone
  - 19 cases associated with anti-TNF therapy and IBD
    - 16 with IFX and AZA/6 MP
      - 15/16 males
      - 6/16 had 1-3 IFX infusion
    - 3 cases with ADA
      - 2 cases with AZA/6 MP

Shale et al. Gut 2008
Natalizumab PML Safety Update: March 2010

- 26 cases of JC virus related PML
  - 25 MS
  - 1 CD
- Total exposure
  - >60,000 pts have received natalizumab
  - >13,000 pts have been treated for more than 2 years
  - Rate of PML 1/1,000 after one year
  - No cases reported in first year of rx
Biologic Questions in Clinical Practice

- Which patient should be started on biologic therapy?
  - Moderate to severe Crohn’s or UC failing conventional therapy or
  - Crohn’s patient at high risk for disability
- When should a patient be started on biologic therapy?
  - Earlier probably better—at minimum should escalate up treatment pyramid
- Which biologic agent should I chose?
  - Anti-TNF agents ~ equivalent
  - Patient choice
  - Reserve natalizumab for anti-TNF refractory patients
- How do you optimize biologics over the long term?
  - Load anti-TNF and continue maintenance
- What do you do when a patient is losing response to therapy?
  - Adalimumab and certolizumab are efficacious
  - Consider natalizumab
  - Surgery?
- Which patients should be treated with concurrent immune suppressants?
  - Consider dual immune suppression in high risk patients
- How do you counsel patients on the risks of therapy?
  - Patients should be aware of serious risks associated with treatment
  - Absolute risks of therapy are low