Choosing Among the Biologic Agents for Inflammatory Bowel Disease

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Objectives and Disclosures

- Objectives
  - To understand the effectiveness and toxicity of the four biologic agents approved for use in Crohn’s disease
  - To identify the features of the biologic agents for Crohn’s disease that would lead to choosing one over the other

- Disclosures - Advisory board/speakers bureau
  - Abbott
  - UCB
  - Shire
  - Salix
  - Warner Chilcott
  - Prometheus
40-Yr-Old Man With Long-Standing Ileocolonic Crohn’s Disease

- S/P 2 ileocecal resections
- Recurrent inflammatory disease in small and large bowel, no stricture or fistula
- Diarrhea and abd pain despite steroids & AZA 2.5 mg/kg (6-TG 260)
- Treated with infliximab
  - 1st infusion - excellent response
  - 2nd infusion – mild acute infusion reaction, excellent response
  - 3rd infusion -
    - Pretreated with steroids, diphenhydramine, & acetaminophen
    - Flushing and headache
    - Response lasted ~4 wk
Potential Mechanisms for Secondary Loss of Response to Anti-TNF

- Antibodies against biologic
- Increased clearance of biologic
- Non-inflammatory complication
Construct of Biologic Agents for the Treatment of Crohn’s Disease

Infliximab
Chimeric mouse–human IgG1 monoclonal antibody

Adalimumab
Human IgG1 monoclonal antibody

Certolizumab pegol
Humanized Fab’ fragment linked to 2 PEG molecules

Natalizumab
CDRs grafted from murine antibody
Humanized IgG4 framework

CDR = complementarity-determining regions; PEG = polyethylene glycol

Adapted with permission from Melmed GY et al. Nature Reviews Drug Discovery. 2008;7:641
Infliximab for Maintenance of Remission at 1 Yr (ACCENT I)

Remission at wk 54\(^1\)

Sustained remission through wk 54\(^2\)

\(P = .007\)

ACCENT = A Crohn's disease Clinical trial Evaluating infliximab in a New long-term Treatment regimen

Infliximab for Maintenance of Remission: Crohn’s Disease-Related Surgeries in ACCENT I

Adapted with permission from Rutgeerts P et al. Gastroenterology. 2004;126(2):402
Adalimumab for Maintenance of Remission at 1 Yr (CHARM)

*P ≤ 0.008 vs placebo

CHARM = Crohn's trial of the fully Human antibody Adalimumab for Remission Maintenance

Adapted with permission from Colombel JF et al. Gastroenterology. 2007;132(1):52
Evaluation of Adalimumab on the Risk of Hospitalization in Patients With Crohn’s Disease: Kaplan-Meier–CD-Related Hospitalization in all Randomized CHARM Patients

N=778

*The difference in hospitalization risk was apparent 2 wk after randomization

Log-rank test for equality over strata showed that hospitalization risk of patients on placebo was significantly different from the risk of patients on adalimumab (P<.01)

PRECISE II: Certolizumab for Maintenance of Remission at Wk 26 in Wk-6 Responders

PRECISE = PEGylated Antibody Fragment Evaluation in Crohn’s Disease

Adapted with permission from Schreiber S et al. N Engl J Med. 2007;357(3):239
Need for Dose Escalation With Infliximab

- Completed Maintenance
- Crossed Over to Episodic
- Discontinued Therapy

- Episodic therapy
- Infliximab 5 mg/kg
- Infliximab 10 mg/kg

Need for Dose Escalation with Adalimumab for Patients NOT in Remission at Wk 4

At 1 yr, 131 patients continued to receive adalimumab
54% received 40 mg EOW
46% dose escalated to 40 mg weekly

CDAI = Crohn’s Disease Activity Index

GAIN: Response and Remission at Wk 4

GAIN = Gauging Adalimumab efficacy in Infliximab Nonresponders

GAIN vs CLASSIC I: Wk-4 Efficacy in Naïve vs Previously-Exposed Patients

CLASSIC = Clinical Assessment of Adalimumab Safety and efficacy Studied as an Induction therapy in Crohn's disease

CHARM: Remission at Wk 56 in Wk-4 Responders

PRECISE II: **Response at Wk 26 in Wk-6 Responders**

![Bar chart showing response rates for Infliximab Naïve and Prior Exposure groups.](chart)

- **Infliximab Naïve**
  - Placebo: 40
  - Certolizumab 400 mg: 69
  - *P* < .001

- **Prior Exposure**
  - Placebo: 26
  - Certolizumab 400 mg: 44
  - *P* = .018

Long-Term Evolution of Disease Behavior in Crohn’s Disease

Adapted with permission from Cosnes J et al. Inflamm Bowel Dis. 2002;8(4):244
SONIC = Study of Biologic and Immunomodulator Naive Patients In Crohn's Disease

Infliximab for Prevention of Postoperative Recurrence

Crohn’s disease patients with surgical resection of the ileum with an ileocolonic anastomosis

N=23; within 4 wk of surgery, patients received study drug at 0, 2, 6 wk then Q 8 wk for 1 yr

AGA Consensus Development Panel on Use of Biologics: Comparative Toxicities of Anti-TNF Agents

- All anti-TNF therapies share similar AEs, including
  - Risk of infection
    - Notably intracellular pathogens (TB & histoplasmosis)
  - Autoimmunity
    - Newly positive ANA, rare drug-induced lupus
  - Infusion reactions (infliximab)
  - Injection-site reactions (adalimumab, certolizumab pegol)
  - Demyelinating disorders (MS & optic neuritis)
  - Congestive heart failure
  - Cancer (non-melanoma skin cancer, non-Hodgkins lymphoma, hepatosplenic T-cell lymphoma)

AE = adverse drug event; ANA = antinuclear antibody
Clark M et al. Gastroenterology. 2007;133(1):312
AGA Consensus Development Panel on Use of Biologics: Contraindications for Anti-TNF Agents

- Known hypersensitivity, if severe
- Active infection
- Untreated latent tuberculosis
- Pre-existing demyelinating disorder
- Moderate-to-severe congestive heart failure
- Current or recent malignancy, without advice from oncologist
- Uncontrolled infusion reactions
- Any anti-TNF should be discontinued when
  - There is no response to induction therapy
  - Duration of response decreases to an economically impractical time
    - <1 wk with adalimumab
    - <2 wk with certolizumab
    - <4 wk with infliximab
Choosing Among the Anti-TNF Agents

Similar efficacy, but effectiveness is best in biologic-naive patients
Similar class-effect AEs, like infection and malignancy.

<table>
<thead>
<tr>
<th></th>
<th>Administration</th>
<th>Reactions</th>
<th>Crosses placenta</th>
<th>Cost</th>
<th>Antibody availability</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infliximab</strong></td>
<td>IV Q8W</td>
<td>~10%</td>
<td>+</td>
<td>Highest</td>
<td>+</td>
</tr>
<tr>
<td><strong>Adalimumab</strong></td>
<td>SQ Q2W</td>
<td>~20%</td>
<td>+</td>
<td>Intermediate</td>
<td>-</td>
</tr>
<tr>
<td><strong>Certolizumab</strong></td>
<td>SQ Q4W</td>
<td>~1%</td>
<td>-</td>
<td>Intermediate</td>
<td>-</td>
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</tbody>
</table>
40 yo man who is a secondary non-responder to infliximab. What is next?

- A. Increase the dose of infliximab
- B. Switch to adalimumumab or certolizumab
- C. Switch to natalizumab
- D. Check a colonoscopy and view of the terminal ileum
- E. Measure ATIs and infliximab levels
Assessing Loss of Response

Reassess for inflammatory signs and symptoms (eg, CRP, colonoscopy, radiology)

- Activity (eg, inflammation)
  - Antibodies to infliximab
- No disease activity (eg, stricture, short bowel, IBS)
  - Surgery; symptomatic treatment
Assessing Loss of Response, cont.

- Antibodies to infliximab
  - (+) Alternative anti-TNF: Adalimumab, Certolizumab
  - (−) No infliximab: Reduce infusion interval or increase dose (10 mg/kg)
  - (−) Infliximab present: Natalizumab
Clinical Utility of Infliximab Levels & Antibodies

- Medical records of 155 IBD pts who had antibodies & levels drawn in clinical practice
- HACAs (23%) – change to another anti-TNF led to complete/partial response in 92%
- Low infliximab (44%) – dose escalation led to complete/partial response in 86%
- Therapeutic infliximab (33%) – no evidence of active inflammation in 62%

40-Yr-Old Man With Long-Standing Ileocolonic Crohn’s Disease, cont.

- Colonoscopy showed active inflammation in the neo-terminal ileum
- ATIs positive
- Patient was prescribed adalimumab
  - 160 mg at wk 0; 80 mg at wk 2; 40 mg EOW
- He responded with resolution of diarrhea & abdominal pain
Case 1: Summary

• Loss of response to infliximab should prompt an investigation to confirm ongoing active inflammation

• For patients who respond to anti-TNF therapy & then lose response or become intolerant:
  – Switching within the anti-TNF class is reasonable if antibodies to infliximab are present
  – Dose escalation is reasonable if antibodies & drug are absent in the blood
  – Switching to natalizumab is reasonable if antibodies are absent & infliximab is present in the blood

• Absolute likelihood of response to second anti-TNF agent is lower than response in naïve patients
56-Yr-Old Woman With Crohn’s Colitis for 5 Yr

- 12–15 stools per day, occasional incontinence
- Currently on pred 30 & AZA 2.3 mg/kg
- 1 Y ago, infliximab 5 mg/kg at wk 0, 2, & 6 with no response
- 6 M ago, treated with certolizumab 400 mg at wk 0, 400 mg at wk 2, then 400 mg every 4 wks; no response.
- Colonoscopy - Deep linear ulcers in the rectum and through much of the colon; terminal ileum normal
- Stool for Clostridium difficile negative
- Mucosal biopsy for cytomegalovirus negative
Primary non-responders to infliximab should:

- A. Have the dose of infliximab increased
- B. Switch to adalimumab or certolizumab
- C. Have ATIs & infliximab levels checked
- D. Consider natalizumab
Endothelial and Leukocyte Adhesion: $\alpha_4$ Integrins

1. Adhesion and Extravasation

2. Activation

$\alpha_4\beta_1$ (VLA-4)

Endothelial Cells

Reactive Oxygen Intermediates, etc

Extracellular Matrix (ECM)
Selective Adhesion Molecule Inhibition

White blood cell

\[ \alpha 4 \beta 1 \text{ (VLA-4)} \]

Blood Vessel
Endothelium
Gut Tissue

Chemoattractant Signal

Blood Vessel
Endothelium
Gut Tissue

Natalizumab

Reduced Gut Inflammation
Natalizumab Approvals

**US Approval:**
- Monotherapy
- "Relapsing forms of MS," to delay disability and reduce frequency of relapses
- Mandatory registry to receive natalizumab

**EU Approval**
- Monotherapy, "relapsing remitting MS"
- No required registry

2004 2005 2006 2007 2008 2009

- **Nov 2004:** Approval by US FDA

- **February 2005:** Voluntarily withdrawn by manufacturer due to PML
  - Biogen Idec share price falls 43%
  - Elan share price falls 70%
  - $17 Billion market capital evaporates

- **June 2006:** Re-approved by US FDA and approved by European Medicines Agency

- **September 2006:** Approved by Health Canada

- **January 2008:** Approved by US FDA for moderately to severely active Crohn’s disease

- **Current Use:** 35,500 patients worldwide
# AGA Consensus Development Panel on Use of Biologics: Natalizumab Dosing and Contraindications

<table>
<thead>
<tr>
<th>Dosing</th>
<th>Contraindications</th>
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<tbody>
<tr>
<td><strong>Induction</strong>  &lt;br&gt;• 300 mg IV give at wk 0, 4, and 8</td>
<td>• Known hypersensitivity, if severe</td>
</tr>
<tr>
<td><strong>Maintenance</strong>  &lt;br&gt;• 300 mg IV every 4 wk for responding patients</td>
<td>• Active infection</td>
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<td></td>
<td>• Current or past progressive multifocal leukoencephalopathy (PML)</td>
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56-Yr-Old Woman With Crohn’s Colitis for 5 Yr, cont.

- Treatment
  - AZA discontinued; prednisone 30 mg continued
  - Initiated natalizumab 300 mg every 4 wk
    - Wk 4—stool frequency decreased to 6 stools/day
      - Prednisone dose reduced to 20 mg
    - Wk 12—stool frequency decreased to 3 stools/day
      - Prednisone discontinued
ENCORE: Induction of Remission

Adapted with permission from Targan SR et al. Gastroenterology. 2007;132(5):1672
ENCORE: Remission in Anti-TNF Failures*

*Anti-TNF failure is defined as: 1) no response to initial treatment, or 2) lost response with continued treatment, or 3) discontinuation due to adverse event, or 4) discontinuation due to infusion reaction

All-Cause and CD-Related Hospitalizations in Natalizumab-Treated Patients: Pooled Analysis of ENACT-1 and ENCORE

ENACT = Evaluation of Natalizumab as Continuous Therapy

Sands BE et al. Presented at: Digestive Disease Week; May 17–22, 2008; San Diego, California. Abstract 1039
ENACT-2: Remission at 9 and 15 Mo

*P*.05 vs placebo

ENACT-2: Corticosteroid Elimination


Start ENACT-2

<table>
<thead>
<tr>
<th>Time (mo)</th>
<th>Natalizumab 300 mg (n=67)</th>
<th>Placebo (n=76)</th>
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<tr>
<td>3</td>
<td>58</td>
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</table>

P = .004  P = .003  P < .001  P = .002  P < .001
ENACT-2: Corticosteroid-Free Remission

Natalizumab Exposure Data: Through April, 2011

- Clinical trials and postmarketing experience
  - More than 83,000 patients have been treated
  - 102 confirmed cases of PML (1 with Crohn’s disease – none since the clinical trials)
  - The label includes a table showing that the risk of PML is:
    - 0.3 per 1,000 patients receiving the drug for less than two years
    - 1.5 per 1,000 during the third year of treatment
    - 0.9 per 1,000 during the fourth year.

U. S. Food and Drug Administration.
Progressive Multifocal Leukoencephalopathy

- A. Is uniformly fatal
- B. Is caused by the Jacob-Cruetzfeld virus
- C. Is caused by a virus that is usually acquired in childhood
- D. Cannot be treated with plasmapheresis
PML: Background

• Pathogenesis
  – Caused by JC polyomavirus
    • Infection is asymptomatic and occurs in childhood
    • Virus remains latent
    • Reactivation results in PML

• Clinical presentation
  – Subacute progression of focal neurologic deficits
    • Visual (retrochiasmal)
    • Motor
    • Sensory
    • Cerebellar
  – Cognitive impairment and behavioral abnormalities

Diagnosing PML

- New neurologic symptoms progressing over weeks
  - Cognitive/personality change
  - Hemiparesis
  - Hemifield visual loss
- Refer to neurologist

- MRI lesions are not pathognomonic
  - Clinical and MRI features unlikely confused with MS
- CSF analysis—confirmatory for JC virus

Berger JR. *Curr Neurol Neurosci Rep.* 2007;7(6):461
Treatment of PML

- Plasma exchange
  - 3 exchanges in 1 wk (5 exchanges to ensure all receptor desaturation)
- Antivirals (none known to be effective; considered investigational)

Berger JR. *Curr Neurol Neurosci Rep.* 2007;7(6):461
TYSABRI® (natalizumab) Outreach:
Unified Commitment to Health (TOUCH™)

- Restricted distribution program developed with the U. S. Food and Drug Administration
- Prescribers, infusion-center staff, and patients all involved in risk minimization
  - Only enrolled prescribers and patients can prescribe and receive natalizumab
  - Only authorized pharmacies and infusion centers can dispense and infuse natalizumab

Department of Health & Human Services.
Case 2: Summary

- Natalizumab is effective for moderate-to-severe Crohn’s disease unresponsive to anti-TNF therapy
- Natalizumab is effective for induction and maintenance of remission and steroid sparing
- PML is a rare but serious event
- Benefit-to-risk ratio of natalizumab appears favorable for appropriately selected patients
Final Summary

- Anti-TNF therapy is effective for moderate-to-severe Crohn’s disease
  - Early intervention may improve long-term course
  - Patients who lose response or become intolerant due to immunogenicity can be switched to another agent within class

- Natalizumab is indicated for patients who have a primary nonresponse to anti-TNF therapy or for patients who lose response or develop intolerance to anti-TNF agents