Disclosures
(Last 24 months)

- Consultant and Grant Support:
  - Abbvie
  - Janssen
  - Prometheus
  - Takeda
  - UCB
Biological Therapies in Crohn’s Disease

- Currently available in the U.S.:
  - Anti-TNF:
    - Adalimumab
    - Certolizumab pegol
    - Infliximab
  - Anti-integrin
    - Natalizumab
- Emerging:
  - Anti-IL12/23:
    - Ustekinumab
  - Anti-integrin
    - Vedolizumab

Optimizing anti-TNF Therapy in IBD

1. Choose the right patients
2. Treat early
3. Load appropriately
4. Consider combination therapy for most patients
5. Stick to a strict maintenance schedule
6. Dose adjust to achieve and to maintain control
7. Monitor for disease “drift”
8. In the future (near?): adjust therapy proactively
Anti-TNFα Agents for Crohn’s disease

Infliximab
Adalimumab
Certolizumab pegol

Monoclonal antibody

= murine
= human

PEGylated humanized Fab' fragment containing 2x20 kDa PEG molecules
# Dosing of Anti-TNFα Agents in CD

<table>
<thead>
<tr>
<th>Agent</th>
<th>U.S. Approval</th>
<th>Induction Dosing</th>
<th>Adult Maintenance Dose</th>
<th>Interval Between Maintenance Injections (weeks)</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab¹</td>
<td>CD lumen CD fistula UC</td>
<td>5 mg/kg at 0, 2, and 6 weeks</td>
<td>5 mg/kg (10 mg/kg in responders who lose response)</td>
<td>8</td>
<td>IV</td>
</tr>
<tr>
<td>Adalimumab²</td>
<td>CD lumen UC</td>
<td>160 mg at week 0 followed by 80 mg at week 2</td>
<td>40 mg</td>
<td>2</td>
<td>SC</td>
</tr>
<tr>
<td>Certolizumab pegol³</td>
<td>CD lumen</td>
<td>400 mg at 0, 2, and 4 weeks</td>
<td>400 mg</td>
<td>4</td>
<td>SC</td>
</tr>
</tbody>
</table>

¹ REMICADE (infliximab) Prescribing Information, August 2008, Centocor, Inc., Malvern, PA.
² HUMIRA (adalimumab) Prescribing Information, February 2008, Abbott Laboratories, North Chicago, IL.
³ CIMZIA (certolizumab pegol) Prescribing Information, April 2008, UCB, Inc., Smyrna, GA.

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**When? Earlier is better!**
Treat beyond symptoms to reduce bowel damage and stop disease progression

Treat beyond symptoms to reduce bowel damage and stop disease progression


Adapted from Pariente B, et al. Inflamm Bowel Dis 2011;17:1415–22
**Induction Treatment with anti-TNFα Agents in Crohn’s Disease**

Clinical remission in anti-TNFα naïve patients (ITT) (CDAI ≤ 150)
(for Targan study CDAI < 150)

**REMISSION AT 4 WEEKS**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients (%)</th>
<th>*</th>
<th>NS</th>
<th>NS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Targan**</td>
<td>52.0</td>
<td>*</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Schreiber**</td>
<td>25.9</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>CLASSIC I</td>
<td>18.2</td>
<td>*</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>PRECiSE 1**</td>
<td>26.7</td>
<td>*</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

2. UCB Data on File.

**Maintenance Treatment with anti-TNF-α in CD**

Moderate to Severely Active IBD
Most Failing Immune modulators

**LONGER DURATION OF DISEASE**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients (%)</th>
<th>*</th>
<th>NS</th>
<th>NS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCENT I** IFX</td>
<td>52%</td>
<td>38%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHARM2** ADA</td>
<td>54%</td>
<td>43%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRECiSE 3** Cert pegol</td>
<td>63%</td>
<td>54%*</td>
<td>44%*</td>
<td></td>
</tr>
</tbody>
</table>

Higher Remission Rates with Adalimumab and Certolizumab with Shorter Disease Duration
Post-hoc analyses

Week 26

* p=0.002; ** p<0.001; † p=0.014; ‡ p=0.001; all vs placebo

<2 years: PBO n=23, Adalimumab n=39; 2 to <5 years: PBO n=36, Adalimumab n=57; ≥5 years: PBO n=111, Adalimumab n=233

Schreiber S, et al. DDW 2007. #985
Earlier Use of Anti-TNF Biologic Therapy in Patients With CD Has Better Outcomes

- Claims data assessment
- >3700 patients all who received anti-TNF at some point
- Three groups: “step-up”, IMM to anti-TNF, early TNF (“top-down”)
- Early anti-TNF therapy is associated with:
  - A lower risk of concomitant corticosteroid use
  - Less frequent need for dose escalation of anti-TNF agent
  - Less frequent need to discontinue or switch anti-TNF therapy
  - Fewer CD-related surgeries

Loss of Response Over Time is Also Less Common with Shorter Duration of Disease

Clinical remission over time in ADHERE (NRI): All patients randomized to adalimumab treatment in CHARM who enrolled in ADHERE

- <2 years, n=36
- ≥2 to <5 years, n=63
- ≥5 years, n=229

NRI, non-responder imputation
Prevent immunogenicity

The Challenge of Immunogenicity to Biological Therapies

• Can occur with all biological therapies
• Associated with loss of response and drug reactions
• May be reduced with:
  – Loading dose of drug
  – Concomitant immune-modulatory therapy
  – Maintenance therapy with drug
### Immunogenicity of TNF Antagonists with and without Concomitant Immune Modulators (IMS)

<table>
<thead>
<tr>
<th></th>
<th>Episodic Maintenance</th>
<th>Scheduled Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IMS-</td>
<td>IMS+</td>
</tr>
<tr>
<td>Infliximab¹</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(CD 5 mg/kg)</td>
<td>38%</td>
<td>16%</td>
</tr>
<tr>
<td>(CD 10 mg/kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infliximab²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(UC 5 mg/kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(UC 10 mg/kg)</td>
<td></td>
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</tr>
<tr>
<td>Certolizumab³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(PRECISE I)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Certolizumab⁴</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(PRECISE II)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adalimumab⁵</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(RA, all doses)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adalimumab⁶</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(CLASSIC II)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Golimumab⁷</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Who is at risk for anti-drug antibodies?

- The patient receiving episodic therapy
  - Intentional
  - Unintentional: break in therapy due to coverage issues or complication
- “Pseudo-episodic therapy”
  - Sub-therapeutic serum drug levels
  - The patient with drug clearance between doses
- The patient who developed anti-drug antibodies previously

2Rubin DT et al. ACG 2013.

Use combination biological and immunosuppressive therapy in most patients
Why Is Combination Therapy More Effective?

- Multiple mechanisms of disease control
- Reduction in anti-drug antibodies
- Elevation of serum drug levels (greater exposure)
- Other mechanisms/unknown

SONIC: Corticosteroid-free clinical remission at week 26 moderate to severe Crohn’s disease

![Graph showing remission rates for different treatments.](image)

Steroid-free Remission by Infliximab Trough Level
SONIC Week 30 results

Median infliximab concentration

SFR at week 26 by w30 IFX TL

Understand the Drug Exposure-Response Relationship

Dose vs. Exposure

- Dose- what you deliver to a patient
- Exposure- what the patient’s body “sees”
- Can distinguish between mechanism failure and pharmacokinetic issues
  - High dose can be associated with low exposure
  - Low dose may be associated with a high exposure

Factors Affecting the Pharmacokinetics of Monoclonal Antibodies

<table>
<thead>
<tr>
<th>Impact on Pharmacokinetics</th>
<th>Drug Levels (Exposure)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of ADAs</td>
<td></td>
</tr>
<tr>
<td>- Decreases serum mAbs</td>
<td></td>
</tr>
<tr>
<td>- Threefold-increased clearance</td>
<td></td>
</tr>
<tr>
<td>- Worse clinical outcomes</td>
<td></td>
</tr>
<tr>
<td>- Reduces formation</td>
<td></td>
</tr>
<tr>
<td>Concomitant use of IS</td>
<td></td>
</tr>
<tr>
<td>- Increases serum mAbs</td>
<td></td>
</tr>
<tr>
<td>- Decreases mAb clearance</td>
<td></td>
</tr>
<tr>
<td>- Better clinical outcomes</td>
<td></td>
</tr>
<tr>
<td>High baseline TNF-α</td>
<td></td>
</tr>
<tr>
<td>- May decrease mAbs by increasing clearance</td>
<td></td>
</tr>
<tr>
<td>Low albumin</td>
<td></td>
</tr>
<tr>
<td>- Increases clearance</td>
<td></td>
</tr>
<tr>
<td>- Worse clinical outcomes</td>
<td></td>
</tr>
<tr>
<td>High baseline CRP</td>
<td></td>
</tr>
<tr>
<td>- Increases clearance</td>
<td></td>
</tr>
<tr>
<td>Body size</td>
<td></td>
</tr>
<tr>
<td>- High BMI may increase clearance</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>- Males have higher clearance</td>
<td></td>
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mAB, monoclonal antibody; ADA, antidrug antibody
Approach to the loss of Response to anti-TNF

Practical Issues in Approach to Loss of Response

• Did the patient respond initially? (1<sup>o</sup> v 2<sup>o</sup>)
• Are they inflamed?
• Is this a pK issue or a mechanism issue?
  – Drug Levels
• Is it time for a new mechanism of management?
## Interpretation of Drug Levels and Anti-Drug Antibodies
*(in the inflamed patient)*

<table>
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<tr>
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<th>Anti-drug Antibodies</th>
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<td>Absent</td>
<td>Switch treatment mechanism</td>
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<tr>
<td>Elevated</td>
<td>Present</td>
<td>Unclear</td>
</tr>
<tr>
<td>Not elevated</td>
<td>Absent</td>
<td>Adjust dose, interval of infliximab</td>
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Switching Mechanisms: Natalizumab: Subset Analysis from ENACT Remission in Anti-TNF Failures

What happens to the patients who receive natalizumab in the current post-TNF paradigm? Chicago Experience


Monitor your Patient!
Clinical Assessment of Disease Control

- Routine inquiry regarding stability of disease control (stable maintenance between doses)
- Strict adherence to maintenance regimen
- Ongoing laboratory assessment of clinical stability
- Increasing utilization of surrogate markers of inflammatory activity (fecal calprotectin)

How to Monitor the Patient on Anti-TNF Therapy

- CBC, Liver enzymes at periodic intervals (quarterly, then q 6 months if stable)
- Annual TB assessment (test if at risk)
- Emerging concept: therapeutic monitoring
  - Would allow trough level dose adjustments
  - Allows assessment of the patient losing response to therapy
Summary: Biological Therapy for Crohn’s Disease

- **Prioritize:**
  - Choose the right patient and treat early!

- **Maximize:**
  - Minimize immunogenicity (load, combine, maintain)

- **Optimize:**
  - Monitor carefully
  - Consider objective markers of disease control

- **Strategize:**
  - Know what you will do with loss of response
  - Have a long term plan