Welcome

CHARTING A NEW COURSE:
A JOURNEY IN THE LONG-TERM MANAGEMENT OF IBD
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Presented by:

Sponsored by:
CHARTING A NEW COURSE:
A JOURNEY IN THE LONG-TERM MANAGEMENT OF IBD

Special Thanks to:

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Presented by:
Learning Objectives

• Discuss the management of ulcerative colitis with 5-ASAs, differentiate among currently available formulations, and determine when the risks and benefits of steroids justify their use

• Explain the rationale for long-term, continuous treatment of IBD and mechanisms for extending the efficacy of first-line biologic therapy

• Identify reasons for switching biologic agents during the long-term therapy of IBD and the data supporting the efficacy, safety, and tolerability of therapeutic switches
Physician Accreditation Statement:

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of Purdue University College of Pharmacy and the GI Health Foundation. Purdue University College of Pharmacy, an equal access/equal opportunity institution, is accredited by the ACCME to provide continuing medical education for physicians.
Overview

- **Navigating Ulcerative Colitis:**
  - When to use 5-ASAs, immunomodulators, steroids, and biologics

- **Holding Course in Crohn’s Disease:**
  - Maximizing the efficacy of the first biologic in IBD

- **Changing Course in Crohn’s Disease:**
  - When and how do you switch therapies?
  - Can we use antibody measurements to guide therapy?
Introduction

Maria T Abreu, MD
Professor of Medicine
Chief, Division of Gastroenterology
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Miami, FL
Step-up Treatment Pyramid for Ulcerative Colitis

Surgery
- Cyclosporine

Severe

IV Steroids
- Anti-TNFα
- Oral Corticosteroids

Moderate

Mild

Budesonide
- Antibiotics
- Mesalamine

Adapted from Lichtenstein GR et al. *Inflamm Bowel Dis.* 2004;10(suppl 2):S2-S10.
Knowing Which Therapy Combinations Work Best

- Experimental Therapies
- 5-ASAs
- Immuno-modulators
- Biologics
- Steroids
Navigating Ulcerative Colitis

When to use 5-ASAs and steroids

Ellen J. Scherl, MD

Director, Inflammatory Bowel Disease Center
Jill Roberts Associate Professor of Medicine
Weill Medical College of Cornell University
New York-Presbyterian Hospital
New York, NY
• Within 2 years of diagnosis
  – 17% experience colonic hemorrhage
  – 13% experience toxic colitis
• Disease progresses in 54% of patients within 5 years of diagnosis
• Complications highest among pancolitis patients
• 20% to 38% ultimately require proctocolectomy
• Increased risk of colon cancer

Therapeutic Pyramid: Historical Approach to Ulcerative Colitis

**Traditional Approach**
- Patients have to "earn" therapy
- Surgery

**Future Approach**
- Individualized therapy based on patient characteristics
- Assessment of prognosis based on severity or failure of other approaches
- Treatment is based on symptom resolution

**Evolving Approach**
- Treatment to hard endpoints like mucosal healing or surrogates of it
- Newer therapies with favorable safety and side effect profiles
- Appreciation for timing of surgery in the presence of immune suppression
- Distinction between cyclosporine and infliximab for severe/fulminant UC
- Appreciation for the implications of a healed mucosa

Assessing Severity of UC: Determining Severity of UC: When to Select 5-ASAs vs Steroids?

<table>
<thead>
<tr>
<th>Category</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>&lt;4 stools/day ± blood normal ESR no signs of toxicity</td>
</tr>
<tr>
<td>Moderate</td>
<td>≥4 stools/day minimal signs of toxicity</td>
</tr>
<tr>
<td>Severe</td>
<td>&gt;6 bloody stools/day + fever, tachycardia, anemia, elevated ESR</td>
</tr>
<tr>
<td>Fulminant</td>
<td>&gt;10 stools/day, continuous bleeding, toxicity, abdominal tenderness/distension, transfusion requirement, colonic dilation on x-ray</td>
</tr>
</tbody>
</table>

Optimizing Mesalamine Adherence

- Symptoms of UC are frequently unpleasant and distressing\(^1\)

- Although 5-ASA therapy is effective, many patients fail to take their medications as we prescribe, resulting in symptomatic flares\(^2\)

- If you want to modify the natural history of UC, increase adherence
  - The most common reason for a flare is patients discontinue their medications

Adherence is Critical to Prevent Flare

5-ASA Delivery Systems:
The Goal of Therapy is to Deliver Active 5-ASA to Site of Disease

Bacterial cleavage
- Sulfasalazine
- Olsalazine Dipentum™
- Balsalazide Colazal™

pH-dependent systems
- Acrylic polymer coated mesalamine
  - Asacol™
- MMX™ mesalamine
  - Lialda™

Time-release system
- Ethylcellulose-encapsulated mesalamine microspheres
  - Pentasa™

pH and time-release system
- Enteric coating; polymer matrix
  - Apriso™
## Oral 5-ASA Formulations

<table>
<thead>
<tr>
<th>Agent (Trade Name)</th>
<th>Dosage Form</th>
<th>Daily Dose</th>
<th>Delivery Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfasalazine (Azulfidine®; generics)</td>
<td>Tablet: 500 mg</td>
<td>Treatment: 2 x 500 mg TID or QID, Maintenance: 2 g/d</td>
<td>Prodrug cleaved by colonic bacteria to 5-ASA and sulfapyridine (200 mg of 5-ASA)</td>
</tr>
<tr>
<td>Sulfasalazine (Azulfidine EN-Tabs®)</td>
<td>Delayed Release Tablet: 500 mg</td>
<td>Treatment: 2 x 500 mg TID or QID, Maintenance: 2 g/d</td>
<td>Enteric coated to retard disintegration in stomach; prodrug cleaved by colonic bacteria to 5-ASA and sulfapyridine (200 mg of 5-ASA)</td>
</tr>
<tr>
<td>Osalazine (Dipentum®)</td>
<td>Capsule: 250 mg</td>
<td>Maintenance: 2 x 250 mg BID</td>
<td>Prodrug cleaved by colonic bacteria to 5-ASA (225 mg of 5-ASA)</td>
</tr>
<tr>
<td>Balsalazide (Colazal®)</td>
<td>Capsule: 750 mg</td>
<td>Treatment: 3 x 750 mg TID</td>
<td>Prodrug cleaved by colonic bacteria to 5-ASA and 4-aminobenzoyl-β-alanine (262 mg of 5-ASA)</td>
</tr>
</tbody>
</table>

# Oral 5-ASA Formulations

<table>
<thead>
<tr>
<th>Agent (Trade Name)</th>
<th>Dosage Form</th>
<th>Daily Dose</th>
<th>Delivery Mechanism</th>
</tr>
</thead>
</table>
| Mesalamine (Asacol®) | Delayed-release Tablet: 400 mg | **Treatment:** 2 x 400 mg TID (total daily dose 2.4 g)  
**Maintenance:** 4 x 400 mg (total daily dose 1.6 g) | Eudragit S coating dissolves at pH ≥7 |
| Mesalamine (Lialda®) | Delayed-release Tablet: 1.2 g | **Treatment:** 2-4 x 1.2 g QD (total daily dose 2.4-4.8 g/d) | Polymer film coating dissolves at pH ≥7; multi matrix system [MMX technology] prolongs dissolution in colon |
| Mesalamine (Pentasa®) | Controlled-release capsule: 250 and 500 mg | **Treatment and maintenance:** 4 x 250 or 2 x 500mg 4 times daily (total daily dose, 4 g) | Ethylcellulose coating microgranules provide time-dependent release |
| Mesalamine (Apriso™) | Delayed- and extended-release capsule: 375 mg | **Maintenance:** 4 x 375 mg QD (total daily dose 1.5 g) | Delayed- and extended-release enteric coating dissolves at pH ≥6; polymer matrix slows release |

What Do You Do When Your First-line 5-ASA Fails?

• Step up dosage of 5-ASA?
• Switch to another 5-ASA/combine 5-ASAs?
• Escalate therapeutic class?
Oral Mesalamine in Active Ulcerative Colitis

Increasing Dosage of Mesalamine did not Improve Remission or Improvement Rates

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo (n=44)</th>
<th>Mesalamine 1.6 g/d (n=44)</th>
<th>Mesalamine 2.4 g/d (n=43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>In remission</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Improved</td>
<td>3 (7%)</td>
<td>12 (27%)</td>
<td>13 (30%)</td>
</tr>
<tr>
<td>Maintained</td>
<td>17 (39%)</td>
<td>12 (27%)</td>
<td>18 (42%)</td>
</tr>
<tr>
<td>Worsened</td>
<td>23 (52%)</td>
<td>19 (43%)</td>
<td>11 (26%)</td>
</tr>
</tbody>
</table>

ASCEND I and II: 6-Week Data

ASCEND 1

Week 6

Overall Improvement (%)

<table>
<thead>
<tr>
<th>Improvement (%)</th>
<th>n=150</th>
<th>n=137</th>
</tr>
</thead>
<tbody>
<tr>
<td>42%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>39%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P = .57

ASCEND 2

Week 6

Overall Improvement (%)

<table>
<thead>
<tr>
<th>Improvement (%)</th>
<th>n=130</th>
<th>n=124</th>
</tr>
</thead>
<tbody>
<tr>
<td>59.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>71.8%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P = .036

Weeks of Treatment

Asacol 2.4 g/day

Asacol 4.8 g/day

The ASCEND III Study

Treatment Success at Week 6

- 65.5% for 2.4 g/day (N=383)
- 70.2% for 4.8 g/day (N=389)

Treatment success (overall improvement)
(P = .17; 95% CI -11.2 to 1.9)

Multi-Matrix Oral 5-ASA in Mild-to-Moderate Active UC

Clinical Improvement†

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Delayed release 5-ASA 0.8 g tid</th>
<th>MMX 5-ASA 2.4 g q day</th>
<th>MMX 5-ASA 4.8 g q day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 50</td>
<td>40</td>
<td>56</td>
<td>61</td>
<td>65</td>
</tr>
</tbody>
</table>

Remission†

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Delayed release 5-ASA 0.8 g tid</th>
<th>MMX 5-ASA 2.4 g q day</th>
<th>MMX 5-ASA 4.8 g q day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 30</td>
<td>22</td>
<td>33</td>
<td>41</td>
<td>41</td>
</tr>
</tbody>
</table>

† Clinical improvement defined as a drop in the Sutherland Index (UC-DAI) ≥3 points from baseline
‡ Remission defined as a Sutherland (UC-DAI) ≤1 with a score of 0 for rectal bleeding and stool frequency and ≥ 1-point reduction from baseline in sigmoidoscopy score

*P ≤ .05; **P ≤ .01; ***P ≤ .001; NS = not significant vs placebo

Dose Escalation in Patients Failing 5-ASAs: Kruis Study (2002)

What do you do When Your First-line 5-ASA Fails?

• Step up dosage of 5-ASA?
• Switch to another 5-ASA/combine 5-ASAs?
• Escalate therapeutic class?
Oral vs Rectal Mesalamine vs Combination Therapy in Active Distal UC

Maintenance of Remission With Delayed- and Extended-Release Mesalamine 1.5 g Once Daily

Maintenance of remission at 6 months after switching to Apriso (%)

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>Apriso (n=322)</th>
<th>Placebo (n=165)</th>
</tr>
</thead>
<tbody>
<tr>
<td>78%</td>
<td>59%</td>
<td></td>
</tr>
</tbody>
</table>

ITT = intention to treat

P<.001

Lichtenstein GR et al. ACG Annual Meeting 2008.
Formulations Used to Maintain Remission Before Patients Switched to Apriso

- Mesalamine (n=264)
- Sulfasalazine (n=159)
- Balsalazide (n=58)
- Other (n=40)
- Suppositories/Enemas (n=34)
- Olsalazine (n=7)

Zakko S. Digestive Disease Week 2009 Abstract # T1202
<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Drug(s)</th>
<th>Dose</th>
<th>% Reduction in IBD Dysplasia/CRC (OR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pinczowski (1994)</td>
<td>Sulphasalazine</td>
<td>1.5-3 g</td>
<td>62 (0.38)</td>
</tr>
<tr>
<td>Moody (1996)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eaden (2000)</td>
<td>Mesalazine</td>
<td>1.2 g</td>
<td>81 (0.19)</td>
</tr>
<tr>
<td></td>
<td>Various 5-ASA</td>
<td>1.5-4 g</td>
<td>75 (0.25)</td>
</tr>
<tr>
<td>Rubin (2003)</td>
<td>Various 5-ASA</td>
<td>≥1.2 g</td>
<td>72 (0.28)</td>
</tr>
<tr>
<td>Van Staa (2005)</td>
<td>Mesalamine</td>
<td>Various</td>
<td>46 (0.54)</td>
</tr>
<tr>
<td>Bernstein (2003)</td>
<td>Various 5-ASA</td>
<td>Various</td>
<td>NS</td>
</tr>
<tr>
<td>Rutter (2004)</td>
<td>Various 5-ASA</td>
<td>Various</td>
<td>NS</td>
</tr>
<tr>
<td>Terdiman (2005)</td>
<td>Various 5-ASA</td>
<td>Various</td>
<td>NS</td>
</tr>
</tbody>
</table>
5-ASA Safety

- **Renal impairment**
  - Exercise caution when using in patients with known renal dysfunction or history of renal disease

- **Hepatic impairment**
  - Exercise caution when using in patients with liver disease

- **Mesalamine and sulfasalazine-induced acute intolerance syndrome**
  - May be difficult to distinguish from IBD flare

- **Hypersensitivity**
  - May occur with mesalamine or sulfasalazine

- **Pregnancy**
  - Category C (olsalazine, Asacol) or B (all other agents)
Increasing Adherence in UC

Factors Influencing Adherence

- **Patient-related factors**
  - Disease duration and extent
  - Single status
  - Male gender
  - Forgetfulness
  - Unable to see need for medication during remission

- **Economic**
  - Cost of filling Rx

- **Relationship with healthcare professional**
  - Lack of supportive relationship
  - Lack of adequate information/education

- **Medication-related factors**
  - Complicated dosing regimen
  - Fear of side effects
  - Impact of schedule on daily life
  - Large number of tablets

Strategies for Improving Adherence

- Open communication between patients and providers
- Patient education regarding benefits of 5-ASA therapy
- Simplify dosing regimen
  - Individual therapy
  - Tailor regimen to patient’s lifestyle
- Minimize side effects

Kane SV. *Aliment Pharmacol Ther.* 2006;23:577-585.
Summary

Dose Optimization: What is the Evidence?

• Nearly one-third of patients fail to respond to mesalamine
  – May be able to salvage 50% by switching, combining escalating or de-escalating

• Adherence strategies for long-term maintenance and chemoprevention warrant further studies
  – Importance of QD dosing
Probiotics in Ulcerative Colitis?

Patients (n=144) randomized to VSL#3 or placebo for 8 weeks

Percentage of patients with reduction of UCDAI > 50% at week 8

<table>
<thead>
<tr>
<th></th>
<th>VSL#3</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>70%</td>
<td>60%</td>
<td>50%</td>
</tr>
</tbody>
</table>

P = .031

Percentage of patients with reduction of UCDAI of at least 3 points at week 8

<table>
<thead>
<tr>
<th></th>
<th>VSL#3</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>40%</td>
<td>35%</td>
<td>30%</td>
</tr>
</tbody>
</table>

P = .046

Percentage of patients in remission at week 8

<table>
<thead>
<tr>
<th></th>
<th>VSL#3</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>50%</td>
<td>45%</td>
<td>40%</td>
</tr>
</tbody>
</table>

P = NS

What do you do When Your First-line 5-ASA Fails?

- Step up dosage of 5-ASA?
- Switch to another 5-ASA/combine 5-ASAs?
- Escalate therapeutic class?
When to Select Steroids?

- **Wrong diagnosis:**
  - Left-sided Crohn’s colitis /Colitis with proximal disease
  - Ischemia
  - Peri-appendiceal red patch
  - Deep Ulcers: CD?
  - Partially treated colitis: Patchy disease
  - Rectal sparing in UC
  - Common variable immunodeficiency
    (Absence of plasma cells)

- **Concurrent Infection**
  - *C difficile*
  - CMV
Why Select Corticosteroids?  
Short and Long-term Efficacy

1-Month Outcomes*  
(n=63)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Complete Remission 54% (n=34)</th>
<th>Partial Remission 30% (n=19)</th>
<th>No Response 16% (n=10)</th>
</tr>
</thead>
</table>

1-Year Outcomes  
(n=63)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Prolonged Response 49% (n=31)</th>
<th>Steroid Dependent 22% (n=14)</th>
<th>Surgery 29% (n=18)</th>
</tr>
</thead>
</table>

*30 days after initiating corticosteroid therapy  
UC n=185 from 1970-1993  
Adverse Events with Steroids

Tolerability
- Psychosis/Cognitive disorders
- Steroid withdrawal symptoms
- Cushingoid/bruising/acne/edema

Development of adrenal suppression

Infection

Cataracts

Osteoporosis/AVN

Hypertension
Using Steroids in UC Requires an Exit Strategy

- In severe UC:
  - CSA, infliximab, visilizumab, basilixumab or colectomy

- In moderate UC:
  - AZA/6MP or infliximab
Azathioprine for Steroid-Dependent, Active UC

Treatment Success* After 6 Months

- **53%** for AZA 2 mg/kg/d
- **19%** for 5-ASA 3.2 g per day (in 3 divided doses†)

*N=72

*Defined as clinical remission (Powell-Tuck Index Score of 0) and endoscopic remission (Baron Index Score ≤ 1) plus steroid discontinuation. Patients treated with concurrent tapering dose of steroids. †0.8 g at breakfast and lunch and 1.6 g at dinner.

Infliximab for Moderate or Severe Refractory UC: Results of the ACT 1 Study

* $P<.001$ vs placebo; **$P<.005$ vs placebo; †Combined groups.
Infliximab for Moderate or Severe Refractory UC: Results of the ACT 2 Study

Week 8 Clinical response: Placebo 29.3%, Infliximab 5 mg/kg 47.1%, Infliximab 10 mg/kg 60%
Week 30 Clinical response: Placebo 64.8%, Infliximab 5 mg/kg 60.0%, Infliximab 10 mg/kg 69.2%
Week 8 Clinical remission: Placebo 5.7%, Infliximab 5 mg/kg 27.5%, Infliximab 10 mg/kg 33.9%
Week 30 Clinical remission: Placebo 10.8%, Infliximab 5 mg/kg 25.0%, Infliximab 10 mg/kg 35.8%
Week 8 Mucosal healing: Placebo 30.0%, Infliximab 5 mg/kg 60.3%, Infliximab 10 mg/kg 61.7%
Week 30 Mucosal healing: Placebo 30.1%, Infliximab 5 mg/kg 46.3%, Infliximab 10 mg/kg 66.7%
Week 30 Discontinued Steroids: Placebo 3.3%, Infliximab 5 mg/kg 16.8%, Infliximab 10 mg/kg 27.3%

* P < .001 vs placebo; **P < .005 vs placebo; †P = .009 vs. placebo
Conclusions

• 5-ASAs are effective in mild to moderately active disease
  – Changing dose or preparation may help certain patients
  – Chemoprevention benefit and less frequent dosing may increase adherence

• Patients with a more severe presentation or failing 5-ASAs may need corticosteroids
  – Once steroids are prescribed an exit strategy should be in place

• Immunomodulators are effective for achieving a steroid-free remission in UC

• In steroid-refractory and steroid-dependent patients, the role of cyclosporine and a biologic should be considered
Holding the Course: Maximizing the First Biologic in the Long-term Management of Crohn’s Disease

David G. Binion, MD

Co-Director, Inflammatory Bowel Disease Center
Director, Translational Inflammatory Bowel Disease Research
Visiting Professor of Medicine
Division of Gastroenterology, Hepatology and Nutrition
University of Pittsburgh School of Medicine
UPMC Presbyterian Hospital
Pittsburgh, PA
Overview

- Why is biologic durability important in CD management?
- What is the durability of biologic therapy in CD?
- What can optimize durability of biologic therapy for our CD patients?
Overview

- Why is biologic durability important in CD management?
- What is the durability of biologic therapy in CD?
- What can optimize durability of biologic therapy for our CD patients?
• Heterogeneity of CD
• Severe CD phenotypes
Crohn’s Disease: 1960s Historical Perspective

- Limited treatment options: sulfasalazine, prednisone
- No treatment algorithm, limited options available
- Irreversible complications
## Probability of Surgery for CD

<table>
<thead>
<tr>
<th>Years After Diagnosis</th>
<th>1 Surgery</th>
<th>2 Surgeries</th>
<th>≥3 Surgeries</th>
<th>No Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>37</td>
<td>7</td>
<td>5</td>
<td>51</td>
</tr>
<tr>
<td>10</td>
<td>39</td>
<td>11</td>
<td>12</td>
<td>39</td>
</tr>
<tr>
<td>15</td>
<td>34</td>
<td>14</td>
<td>22</td>
<td>30</td>
</tr>
</tbody>
</table>

Severe CD: Rapid Postsurgical Recurrence

Severe CD and Permanent Work Disability

Estimate of work capacity: 10 years following diagnosis

CD Medical Management Algorithm: No Partial Obstruction or Abscess Detected

"Top down" introduction of biologic

SONIC introduction of biologic

**Mild**
- 5-ASA, budesonide or antibiotics

**Moderate**
- Corticosteroid taper
- AZA/6-MP/MTX to induce/maintain remission
  - Yes
    - Breakthrough
      - AZA/6-MP/MTX maintenance
      - Surgical patients
  - No

**Severe**
- Unable to taper corticosteroids
  - Inadequate response to AZA/6-MP/MTX
    - infliximab, adalimumab, certolizumab, natalizumab maintenance
Long-term Medical Management of CD

- Define who cannot tolerate standard immunosuppression
- Define who has failed to respond to standard immunosuppression
- This is a high risk CD phenotype
  - Maximizing the longevity of biologic therapy is essential in this patient subgroup
Azathioprine Intolerance in CD: Rates of Early Adverse Reactions

Rates of Early Adverse Reactions

- 29% Adverse Reactions
- 5% No Adverse Reactions

P = .008

10%: Severe adverse reactions to azathioprine/6MP, including fevers, headache, pancreatitis, respiratory failure, blistering skin lesions within 4 weeks of initiation

Autoimmune Hepatitis
Crohn’s Disease

Biologic Era in IBD Management: Healing of Refractory Ulceration/Fistula With Anti-TNF Agents

The First-line Biologic Agents for the Treatment of CD

Infliximab
Chimeric monoclonal antibody (75% human IgG1 isotype)

Adalimumab
Human recombinant antibody (100% human IgG1 isotype)

Certolizumab Pegol
Humanized Fab’ fragment (95% human IgG1 isotype)

Mouse
Human
PEG, polyethylene glycol.
Overview

• Why is biologic durability important in CD management?

• What is the durability of biologic therapy in CD?

• What can optimize durability of biologic therapy for our CD patients?
Durability of Infliximab for CD

• 50% of CD patients have discontinued infliximab by 6 years of maintenance therapy (n=153)

• >80% of these patients were on combination immunosuppression

• Dose escalation in >50%

• Reasons for discontinuation:
  Allergy/adverse rxn - 44%
  Decreased efficacy - 38%

Holding the Course: Maximizing the First Biologic in CD

Outline

- Why is biologic durability important in CD management?
- What is the durability of biologic therapy in CD?
- What can optimize durability of biologic therapy for our CD patients?
Avoid episodic dosing.
Durability of Infliximab for CD

- 50% of CD patients have discontinued infliximab by 6 years of maintenance therapy (n=153)
- 28.8% of patients with history of episodic dosing discontinued infliximab vs. 11.7% of patients with continuous dosing (p = 0.025)
- Any missed infusion or infusion interval > 8 weeks was counted as episodic dosing

Effect of Prior Episodic Dosing on Long-term Performance of Infliximab Maintenance: Hospitalizations and Surgeries at 3 years

- 40 patients with prior irregular dosing
- 61 patients with scheduled maintenance
- Any missed infusion counted as prior episodic dosing
- Total excess cost in the PI exposure cohort of $11,464 during the third year of infliximab maintenance therapy per patient

P = 0.004

Maintenance Infliximab (IFX) Decreases Long-term Need for Bowel Surgery

<table>
<thead>
<tr>
<th></th>
<th>Scheduled Treatment</th>
<th>Episodic Therapy</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalizations (%)</td>
<td>50 / 194 (26)</td>
<td>165 / 353 (47)</td>
<td>P&lt;.0001</td>
</tr>
<tr>
<td>Median hospitalizations (range)</td>
<td>1 (1-2)</td>
<td>2 (1-4)</td>
<td>P&lt;.0001</td>
</tr>
</tbody>
</table>

Adalimumab: Induction Only/Reinitiated vs Continuous Maintenance Therapy at Week 56


\[ a P < .05, 40 \text{ mg EOW vs IO/R} \]

\[ b P < .05, 40 \text{ mg EW vs IO/R} \]
Concomitant immunosuppression improves efficacy and pharmacokinetics of infliximab
Corticosteroid-Free Clinical Remission at Week 26 in the SONIC Study

Primary Endpoint

Mucosal Healing at Week 26 in the SONIC Study

**Increased infliximab blood levels in patients who take immunosuppressives**

<table>
<thead>
<tr>
<th></th>
<th>No immunosuppressives</th>
<th>Immunosuppressives</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IFX levels</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(median + IQR) AZA MTX</td>
<td>2.42 μg/mL (1–10.8)</td>
<td>6.45 μg/mL† (3–11.6)</td>
</tr>
<tr>
<td>Max IFX</td>
<td>21 μg/mL</td>
<td>33.4 μg/mL</td>
</tr>
</tbody>
</table>

†P=.065

## Immunogenicity of Biologics for IBD

<table>
<thead>
<tr>
<th></th>
<th>Episodic</th>
<th>Scheduled</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IM- (%)</td>
<td>IM+ (%)</td>
</tr>
<tr>
<td></td>
<td>IM- (%)</td>
<td>IM+ (%)</td>
</tr>
<tr>
<td>Infliximab(^1)</td>
<td>38</td>
<td>16</td>
</tr>
<tr>
<td>(CD 5 mg/kg)</td>
<td>11(^*)</td>
<td>7(^*)</td>
</tr>
<tr>
<td>Infliximab(^2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(UC all doses)</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Certolizumab(^3,4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(CD all doses)</td>
<td>No data</td>
<td></td>
</tr>
<tr>
<td>10.9</td>
<td>3.3</td>
<td></td>
</tr>
<tr>
<td>Adalimumab(^5,6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(RA all doses)</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Adalimumab(^7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Classic II only)</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.6(^**)</td>
<td></td>
</tr>
</tbody>
</table>

\(^*\)30% patients on episodic

\(^**\)30% patients on IM\(^3\)

Concurrent Methotrexate Increases Likelihood of Detectable Infliximab Levels

Trough Concentration of Infliximab is Higher With Concurrent Methotrexate

Defining Primary and Secondary Failure

CDAI score

Primary failure

Secondary failure

Remission

0 150 200 250
weeks 4 8 12
weeks

year

0 4 8 12 1
weeks

74
Endoscopic Recurrence Reduced in Infliximab Treated Patients

Infliximab vs placebo

\[ P = 0.0006 \]

30% of the patients in remission were on infliximab prior to surgery and considered “failures”

Endoscopic Recurrence defined as endoscopic scores of i2, i3, or i4.

Fear of medical malpractice litigation may influence gastroenterologists’ use of biologic agents in treatment of CD.
Physician Insurer’s Association of America (PIAA) Medical Malpractice Claims Database

- PIAA is the leading insurer trade association representing insurers in the US
- PIAA provides insurance for 60% of physicians in the US
- PIAA was established in 1977 to collect malpractice claims data
- PIAA closed claims database was queried between 1985 – 2008 evaluating claims involving IBD patients (CD and UC)
Malpractice Claims Against Gastroenterologists Involving IBD Patients

- There were 81 closed claims against gastroenterologists 1985 – 2008
- 19 were paid claims
- Total GI indemnity: $6,174,059
- Most common reasons for litigation against GI physicians:
  - Error in diagnosis: 23%
  - Improper performance: 16%
  - Failure to supervise a case: 8%
  - Medication errors: 7%

1985 - 1998
12 paid claims by GI

1999 - 2008
7 paid claims by GI

IBD Medical Malpractice Claims
Targeting Gastroenterologists

- Occurs rarely and has decreased over the past decade.
- Concern regarding the increased use of immunosuppression and biologic therapy in IBD does not correlate with litigation patterns.
• A subgroup of severe CD patients is at risk for multiple surgeries, permanent work disability
  – These patients may benefit from long-term biologic maintenance therapy
• CD patients who are intolerant to or fail standard immunomodulators are candidates for long-term biologic treatment
• Durability of biologic therapy in CD is limited
  – Episodic dosing diminishes durability.
• Efficacy and durability is improved with standard dosing and concomitant immunosuppression
• Fear of medical malpractice should not influence use of long-term biologic therapy in severe CD patients who warrant therapy
Changing Course
When and how do you switch therapies?

Scott E. Plevy, MD
Associate Professor of Medicine, Microbiology and Immunology
University of North Carolina School of Medicine
Chapel Hill, NC
• Switching biologics: Lessons from rheumatoid arthritis

• When to switch biologics in IBD?

• Efficacy of switching: Clinical data
Switching Biologics: The RA Experience

- Prospective cohort study of new anti-TNF starts (N=6739)

- Over 15 months after initiation of first biologic, 27.7% discontinued treatment:
  - 841 (12.5%) for lack of efficacy
  - 1023 (15.2%) due to toxicity

- Of these, a second biologic was initiated in 46.0%

Switching Biologics: The RA Experience

Drug discontinuation due to inefficacy

Drug discontinuation due to adverse events

Switching Biologics: The RA Experience

The GO-AFTER Study: The first double-blind RCT of switching biologics

• Objective
  – Examine the efficacy and safety of golimumab in patients who had previously received ≥1 prior TNF inhibitor

• Design
  – Patients randomized to 24 weeks of therapy with:
    • Golimumab 50 mg q4w
    • Golimumab 100 mg q4w
  – Patients continued stable doses of methotrexate or other nonbiologic DMARDs, corticosteroids, or NSAIDs

• Patients (N=461)
  – Active RA despite treatment with ≥1 prior TNF inhibitor regimen

• Primary end point
  – ACR20 response

Golimumab was Effective in Some TNF Failures (ACR50 Response)

ACR50 is generally considered a clinically significant response

Switching Biologics: Lessons Learned from the RA Experience

- The majority of patients who start a second anti-TNF agent continue this therapy beyond 6 months.

- In patients who discontinue a second anti-TNF, the reasons for discontinuation are the same as for the first anti-TNF.

- In GO-AFTER, the rates of “clinically meaningful” response (eg, ACR50) were relatively low (16%-20%) with second-line agent.
Overview

- Switching biologics: Lessons from rheumatoid arthritis
- When to switch biologics in IBD?
- Efficacy of switching: Clinical data
## Immunogenicity of TNF Antagonists

### Patients With Detectable Antibodies to a TNF Antagonist

<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 (CD 5 mg/kg)</td>
<td>38%</td>
<td>16%</td>
</tr>
<tr>
<td>Infliximab¹ (CD 10 mg/kg)</td>
<td>8%</td>
<td>No data</td>
</tr>
<tr>
<td>Infliximab² (UC 5 mg/kg)</td>
<td>No data</td>
<td>19%</td>
</tr>
<tr>
<td>Infliximab² (UC 10 mg/kg)</td>
<td>No data</td>
<td>9%</td>
</tr>
<tr>
<td>Certolizumab³ (PRECISE I)</td>
<td>10%</td>
<td>4%</td>
</tr>
<tr>
<td>Certolizumab⁴ (PRECISE II)</td>
<td>24%</td>
<td>8%</td>
</tr>
<tr>
<td>Adalimumab⁵ (RA, all doses)</td>
<td>No data</td>
<td>12%</td>
</tr>
<tr>
<td>Adalimumab⁶ (CLASSIC II)</td>
<td>No data</td>
<td>4%</td>
</tr>
</tbody>
</table>

IMS = immunosuppressant.
Clinical Outcomes at >52 Weeks According to Trough Infliximab Concentration

Clinical Remission

C-reactive Protein

Endoscopic Change

Clinical Outcomes in UC Patients Treated With Infliximab Correlate With Detectable Trough Levels

Adalimumab Trough Levels Predict Long-term Response

SONIC: IFX Trough Levels at Week 30* are Higher with Concomitant AZA

* Patients who had 1 or more PK samples obtained after their first study agent administration were included in the analysis

SONIC: Immunogenicity Results at Week 30

- Patients who had 1 or more PK samples obtained after their first study agent administration were included in the analysis.
- PK data at Wk 30 was not available for 1 patient treated with AZA + placebo.
- 3 patients treated with IFX + placebo.
- 4 patients treated with AZA + IFX.

**Infliximab Serum Levels are Related to Mucosal Healing**

- **Methods**
  - Analysis of serial serum samples

- **Patients**
  - Crohn’s disease on infliximab (N=215)

---

**Graph:**

- **Trough infliximab concentration (µg/mL)**
  - Complete healing: 6.05
  - Partial healing: 3.29
  - No healing: 0.85

*P*= .042

---

Clinical Utility of Measuring Anti-TNF Levels and Human Anti-Chimeric Antibodies

• Objective
  – Evaluate clinical utility of measuring HACA and infliximab concentrations

• Patients (N=155)
  – CD (78%) or UC (20%)

• Methods
  – HACA and infliximab concentrations measured in 155 patients
    • Indications for testing included loss of response (49%), partial response (22%), possible autoimmune reaction (10%)

Clinical Outcomes in Patients With Detectable HACA (n=35)*

- *6 discontinued IFX, 3 continued same dose, 3 proceeded to surgery, 5 patients could not be assessed
Clinical Outcomes in Patients With Sub-therapeutic Concentrations (n=69)*

- 86% response for Infliximab increased (25/29) with complete/partial response
- 33% for Anti-TNF changed (2/6) with complete/partial response

P < .016

* 10 continued same dose, 9 discontinued IFX, 8 proceeded to surgery, and 7 patients could not be assessed

Potential Treatment Algorithm Based on Therapeutic Anti-TNF Agent Concentrations

Positive HACA

- Change to another anti-TNF agent
- Increase IFX dose

If no response, change to Rx with different mechanism of action (non-anti-TNF agent)

Potential Treatment Algorithm Based on Therapeutic Anti-TNF Agent Concentrations

Subtherapeutic infliximab concentration

- Increase infliximab dose or frequency
  - If no response, change to different anti-TNF agent

- Change to different anti-TNF agent
  - If no response, change to Rx with different mechanism of action (non-anti-TNF agent)

Potential Treatment Algorithm Based on Therapeutic Anti-TNF Agent Concentrations

* Therapeutic infliximab concentration

- Endoscopy/CTE with active disease
- Endoscopy/CTE with inactive disease

* Patients should have endoscopic or radiologic imaging

Change to Rx with different mechanism of action (non-anti-TNF agent)

Investigate for alternate etiology of symptoms

Long-Term Benefit Of Infliximab Therapy

Median Follow-Up Of 41 Months

585 Patients

46% - Episodic switched to q 8 week maintenance

19.7% - Reduction in interval of infusions
26.3% - Increase in dose
3.8% - Reduction and Increase

~70% who increased dose were able to go back to 5 mg/kg q 8 weeks (only 28.7% with shortened interval could go back to q 8 weeks)

Sustained Clinical Benefit of Infliximab In 349/548 Patients (64.3%)

Schnitzler et al. Gut. 2009
Overview

• Switching biologics: Lessons from rheumatoid arthritis

• When to switch biologics in IBD?

• Efficacy of switching: Clinical data
Adalimumab: Week 4 Remission by Prior Anti-TNF Exposure

Clinical remission was defined as a decrease in the Crohn’s Disease Activity Index score to <150 points at week 4.

Certolizumab Pegol: Week 26 Clinical Remission by Prior Anti-TNF Exposure

**PRECiSE 2**

- Certolizumab pegol (3 injections) + placebo
- Certolizumab pegol 400 mg

Clinical remission: CDAI ≤150 points

WELCOME Study: Response and Remission with Certolizumab by Reason for Discontinuation of First Agent

<table>
<thead>
<tr>
<th></th>
<th>Certolizumab response&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Certolizumab remission&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>61.0</td>
<td>39.3</td>
</tr>
<tr>
<td>N=539</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intolerance to infliximab</td>
<td>62.3</td>
<td>45.7</td>
</tr>
<tr>
<td>n=199</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss of response to infliximab</td>
<td>61.2</td>
<td>35.9</td>
</tr>
<tr>
<td>n=304</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intolerance and loss of response to infliximab</td>
<td>57.6</td>
<td>30.3</td>
</tr>
<tr>
<td>n=33</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> ≥100-point decrease in CDAI score;  <sup>b</sup> ≥150-point decrease in CDAI score.
Abreu M et al. Presented at: Scientific Meeting of the American College of Gastroenterology, October 5-8, 2008; Orlando, Florida.
Data Gaps

• Should IFX levels impact upon clinical decisions?
  – Need prospective comparative data to decide
Proposed Study

Clinical Arm

Lost IFX response

Dose escalate
Switch

IFX Level Arm

Lost IFX response

Low IFX level
Dose escalate
Switch

No IFX level
Switch

Normal IFX level
Dose escalate
Switch

Switch
If a patient loses response and/or develops immunogenic complications....

- Combination therapy is **mandatory** with the second TNF inhibitor because:
  - We are exhausting limited options
  - Response to the second TNF inhibitor may not be as good as the first
  - Patients may be genetically predisposed to developing antibodies to biologics
Key Takeaways

Maria T Abreu, MD
Professor of Medicine
Chief, Division of Gastroenterology
University of Miami Miller School of Medicine
Miami, FL
Key Takeaways (I)

• 5-ASAs are highly effective in mild-to-moderate ulcerative colitis
  – Patients may need dose adjustments or occasionally a switch to a different preparation
  – Less frequent doses increase adherence
  – Chemoprevention benefit has been demonstrated

• Patients with symptoms in spite of 5-ASAs or with more severe symptoms need corticosteroids (ulcerative colitis)
  – Exit strategy includes immunomodulators or biologics
  – No benefit of probiotics in this situation
Key Takeaways (II)

- **Anti-TNF therapy for Crohn’s disease or ulcerative colitis**
  - “It’s never as good as the first time”
  - In most situations, concurrent immunomodulators should be used

- **Patients may have waning response to biologic**
  - Checking levels of biologic or antibodies to the biologic may help edify the reason for loss of response
  - Changing to a different anti-TNF is best in patients with high antibodies to infliximab
  - Randomized controlled trials needed in this arena
Thank you!

Q&A Session