INFLAMMATORY BOWEL DISEASE FORUM

Front-line Issues in Diagnosis & Management

SATURDAY, NOVEMBER 23, 2013

CO-COURSE CHAIRS
Stephen B. Hanauer, MD
Gary R. Lichtenstein, MD
Ulcerative Colitis:
Defining Extent of Disease

- Ulcerative proctitis (rectum only)
- Left-sided colitis (extends to splenic flexure or ≤ 60 cm)
- Extensive colitis (beyond splenic flexure or > 60 cm)
Ulcerative Colitis Therapies

- Biologics
- Immunomodulators
- Corticosteroids
- Aminosalicylates
- Antibiotics?
- Budesonide

Choosing the Right 5-ASA

• Location of disease
• Previous experience with 5-ASA
• Combination therapy (oral + topical)
• Dose
• Compliance
5-ASA Release Sites

- Pentasa (Mesalamine CR)
- Apriso (Mesalamine ER)
- Delzicol (Mesalamine DR)
- Asacol-HD (Mesalamine DR)
- Mezavant XL (Mesalazine)
- Azulfidine (Sulfasalazine DR)
- Colazal (balsalazide 750 mg)
- Giazo (balsalazide 1.1 g)
- Dipentum (Olsalazine)

Mechanisms of Release:

- Pentasa: Moisture
- Apriso: pH ≥ 6; Moisture
- Delzicol, Asacol-HD: pH ≥ 7; Moisture*
- Azulfidine, Colazal, Giazo, Dipentum, Enema Suppository: Azo-bond (orals) Directly applied (topicals)

* Mezavant utilizes both Moisture and Azo-bond

Sources: FDA package inserts / company websites.
Previous 5-ASA Problems?

- Intolerance to specific 5-ASAs?
- Intolerance to similar 5-ASAs?
  - i.e., same coating on Delzicol, Asacol HD, and Lialda (mesalamine DR)
- Intolerance to all 5-ASAs?
  - Even topicals?
Active Left-sided UC: Combination Therapy Superior to Solo Therapy with Oral Mesalamine, 2.4 g, or Mesalamine Enemas, 4.0 g

Percent of patients reporting no blood seen in stool

Remission Maintenance UC: Combination Therapy Superior to Solo Therapy with Oral Mesalamine, 1.6 g

72 patients with UC (greater than proctitis) in remission x 1 month, at least 2 relapses in past year

5-ASA oral (1.6 g/d) + 5-ASA enemas (4 g/d)

Double-blind randomized

5-ASA oral (1.6 g/d) + placebo enemas

12 months

Relapse rate 39% ($P<0.05$)

12 months

Relapse rate 72%

Induction of Response:
2.4 g to 4.8 g/day

Adapted from:
Induction of Response: 2.4 g to 4.8 g/day

Patients in Remission (%)

*P = 0.001; †P < 0.01; both comparisons vs. placebo.

P ≤0.01 for all comparisons vs. placebo.

Adapted from:
Patients Who Stay on 5-ASA:

Cost **LESS** than those who do not:

- 31% lower *unadjusted* mean annual costs
- 54.4% lower adjusted mean *medical* costs
- 27.65% lower adjusted *total* costs

Rationale for Antibiotic Therapy in IBD

- ↓ Luminal bacterial concentrations
- Selectively eliminate bacterial subsets
- ↓ Tissue invasion, microabscesses
- ↓ Bacterial translocation, systemic dissemination
Results of UC Antibiotic Trials

**Ulcerative Colitis**

- Metronidazole
  - Mixed data
- Ciprofloxacin
  - Mixed data
  - Benefits during steroid therapy
- Rifaximin
  - Uncontrolled data suggests potential efficacy

**Pouchitis**

- Ciprofloxacin
  - Effective alone or in combination with other antibiotics
- Metronidazole / Tinidazole
  - Effective alone or in combination with other antibiotics
- Rifaximin
  - Effective alone or in combination with other antibiotics.

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Budesonide

• Highly potent steroid
• Undergoes extensive hepatic 1\textsuperscript{st} pass metabolism
  – Only 10\% systemic steroid exposure
  – Very few steroid-related adverse effects
• Ideally: targeted delivery to the inflamed bowel
Topical Corticosteroids

- Hydrocortisone Enema (100 mg):
  - Easier to retain than 5-ASA enema
  - Systemic absorption approximately 40%
- Hydrocortisone Foam (10%)
  - Secret weapon for difficult-to-treat distal disease
- Budesonide Enema
  - Efficacious; minimal corticosteroid side-effects
- Budesonide Foam
  - Efficacious; little/no corticosteroid side-effects
- Hydrocortisone Suppositories
Mild-to-Moderate UC: Summary

- Aminosalicylates
  - Match release to disease location
  - ? Previous experience with 5-ASA
  - Dual therapy if needed
  - Dose optimization
  - Compliance is paramount!

- Antibiotics
  - Limited data in UC
  - Useful in pouchitis

- Budesonide
  - Induction of response/remission
  - Maintenance ?
Ulcerative Colitis: Treatment Options and Considerations for Moderate-to-Severe Disease

Miguel Regueiro, MD
Professor of Medicine
Associate Chief for Education
Clinical Head and Co-director, IBD Center
University of Pittsburgh School of Medicine
Definitions of Clinical Severity of Disease

We do not include endoscopy in current rating of severity

MILD

<4 stools/day ± blood
Normal ESR
No signs of toxicity

MODERATE

≥ 4 stools/day
Minimal signs of toxicity

SEVERE

>6 bloody stools/day + fever, tachycardia, anemia, or ↑ ESR

FULMINANT

>10 stools/day, continuous bleeding, toxicity, abdominal tenderness/distension, transfusion requirement, colonic dilation on x-ray

UC Medications

- 5-Aminosalicylates
- Bacterial-modifying agents
  - Antibiotics and probiotics
- Corticosteroids
  - Systemic vs. topically active
- Immunomodulators
  - Azathioprine/6-Mercaptopurine, Methotrexate
- Biologic response modifiers (eg, anti-TNFs)
  - Infliximab, Adalimumab, Golimumab
## Steroid Therapy in IBD – Olmsted County

### All patients with IBD 1970 to 1993

<table>
<thead>
<tr>
<th></th>
<th>CD (n = 173)</th>
<th>UC (n = 185)</th>
</tr>
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<tbody>
<tr>
<td>Steroid therapy</td>
<td>43% (74)</td>
<td>34% (63)</td>
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<tr>
<td>Therapeutic response*</td>
<td></td>
<td></td>
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<tr>
<td>Response</td>
<td>58% (43)</td>
<td>54% (34)</td>
</tr>
<tr>
<td>Partial response</td>
<td>26% (19)</td>
<td>30% (19)</td>
</tr>
<tr>
<td>No response</td>
<td>16% (12)</td>
<td>16% (10)</td>
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</tbody>
</table>

*30 days after initiating steroid therapy

Steroid Therapy in IBD – 1-year Outcome
Olmsted County

CD
- 38% Prolonged response (n=31)
- 32% Steroid dependent (n=14)
- 28% Surgery (n=18)

UC
- 29% Prolonged response (n=31)
- 22% Steroid dependent (n=14)
- 49% Surgery (n=18)

Primary Endpoint

* Statistically significant vs. placebo

AZA vs. 5-ASA in Patients with Steroid-Dependent UC

Clinical and Endoscopic Remission and Steroid Withdraw at 6 mos.

Randomized single-blind controlled trial of 67 steroid dependent UC patients
AZA: Azathioprine
5-ASA: 5-aminosalicylic acid

Algorithm for Induction and Maintenance of Remission in Moderate Ulcerative Colitis

- Flare with mild-to-moderate activity
  - 5-ASA +/- local therapy
  - Remission
  - Maintenance therapy 5-ASA
  - Surgery
    - Colectomy and ileoanal pouch procedure

- Flare with moderate-severe activity
  - Oral/IV steroids +/- oral 5-ASA
  - Remission
  - Severe activity
  - Immunomodulator for induction and maintenance of remission:
    - Azathioprine, 6-MP, Infliximab or Adalimumab

- Recurrence after steroid induction; Steroid-dependent/refractory course
  - Continued activity
  - Infliximab, Cyclosporine or Tacrolimus
Case

- 37-year-old male with pan-UC x 5 years and recent *Clostridium difficile*
- *C. difficile* treated and now negative but having flare
- 20 bloody BMs per day despite 40 mg of prednisone and 4.8 g/d mesalamine
- 6-MP one year ago caused pancreatitis
- Hgb 9.0, CRP elevated, and ill-appearing in office
- Decision is made to admit to the hospital
- Unprepped flex sig shows:
Clinical Algorithm Severe, (Oral) Steroid-Refractory UC

KUB if suspicion of toxic megacolon, unprepped flexible sigmoidoscopy to determine diagnosis and severity of disease

Exclude CMV
Exclude Clostridium difficile

IV steroids plus IV antibiotics 1 to 3 days

No response or partial response

Consult with surgeon!!!

IV Cyclosporine

IV Infliximab
? Adalimumab?

Colectomy

No or partial response
Summary

• ~50% of UC patients respond to corticosteroids and may be maintained on 5-ASA

• For moderate-to-severe outpatient UC
  – Thiopurines – limited benefit, do not prolong if no response in 2 m
  – Methotrexate – possible benefit, results of 2 studies forthcoming
  – Anti-TNF – definite benefit

• For severe-to-toxic inpatient UC
  – Anti-TNF: colon acts as “TNF sink” – higher-dose anti-TNF?
  – Cyclosporine – reasonable for pt. naïve to thiopurines
  – Surgery

• I still like sulfasalazine and do not forget about this medication!
Ulcerative Colitis Non-responders

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Ulcerative Colitis Non-responders

- Establish the Correct Diagnosis, Severity of Disease, and Extent of Disease
- Evaluate for Disease Complications
- Evaluate for Enteric Infections
- Use Optimal Medication Doses
- Switch Medications- Different Mechanism
- Miscellaneous
  - NonAdherence
  - Paradoxical Responses
  - NSAIDs
  - Cigarettes
Anti-TNF Agents Approved for UC

- Infliximab
- Adalimumab
- Golimumab
- Certolizumab pegol
Ulcerative Colitis: When to Introduce Anti-TNF Therapy

Ulcerative Colitis (UC)
- Steroid Refractory UC
- Steroid Dependent UC
- Immunomodulator Refractory or Intolerant UC
- Clinical predictors of a poor outcome at diagnosis?
Ulcerative Colitis: Dosing of Anti-TNF Therapy

I. **Infliximab**
   - 5 mg/kg at 0, 2, 6 weeks then every 8 weeks
   - Dose escalation to 10 mg/kg up to every 4 weeks maximum

II. **Adalimumab**
   - 160 mg at 0 then 80 mg at 2 wks then 40 mg sq every 2 weeks
   - Dose escalation to 40 mg sq weekly*

III. **Certolizumab Pegol**
   - 400 mg sq at 0 then 400 mg at 2 wks then 400 mg sq every 2 weeks
   - Extra single 400 mg sq dose at week 3*

IV. **Golimumab**
    200 mg sq at 0 then 100 mg at 2 weeks then 100 mg every 4 weeks

*Not FDA Approved
Management of Severe Ulcerative Colitis

Severe Disease

Despite optimal dose of

- Steroids orally (40 to 60 mg of prednisone)
- Aminosalicylates (oral) and/or
  - Aminosalicylates (topical)

Parenteral steroids equivalent of 300 mg IV of hydrocortisone
Steroids: Predictors of Failure in Ulcerative Colitis

- Steroid failure at Day 3:
  - Sustained fever
  - Persistence of diarrhea (>4 BM/d)
  - CRP elevation

- In multivariate analysis:
  - Blood in stools
  - >6 BM/d

Consider earlier - alternate medical therapy or surgical therapy

Current Therapeutic Options for Hospitalized UC Patients

- IV Corticosteroids
- Cyclosporine*
- Infliximab
- Tacrolimus*
- Surgery*

*Not FDA-approved for ulcerative colitis

Immunogenicity

Three potential strategies alone or in combination to lessen immunogenicity to anti-TNF agents and thus lessen the potential for drug resistance

- Concomitant immunosuppressant
  - AZA, 6-MP, MTX
- Induction and maintenance dosing of anti-TNF therapy - NOT on demand
- Premedication with hydrocortisone 200 mg IV
Management Algorithm for Loss of Response to Anti-TNF Agents

Loss of response to 1st anti-TNF agent

Evaluate for:
- Objective evidence of inflammation
- Exclusion of complications, such as stricture, abscess, infection

Inflammation present
No complication

Inflammation absent
No complication

Inflammation absent
complication

1st agent = infliximab: Consider checking infliximab and antibody to infliximab levels

ATI Low
Low serum infliximab
Increase dose and/or decrease interval

ATI High
Low serum infliximab
Increase dose and/or decrease interval
OR
Switch to 2nd anti-TNF

ATI Low
Adequate serum infliximab

1st agent = adalimumab or certolizumab pegol

ATI Low
Low serum infliximab

ATI High
Low serum infliximab
Increase dose and/or decrease interval
OR
Switch to 2nd anti-TNF

Specific treatment for complication

Symptomatic therapy for presumed irritable bowel-like symptoms
Crohn’s Disease: Treatment Options and Considerations for Mild-to-Moderate Disease

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Professor of Medicine
Associate Chief for Education
Clinical Head and Co-Director, IBD Center
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Disease Severity

- **Severe-to-Fulminant**
  - Failed Rx
    - High fever, cachexia, peritoneal signs, persistent vomiting, obstruction, abscess

- **Moderate-to-Severe**
  - Failed treatment for mild-moderate
    - Fevers, anemia, abdominal pain/tenderness, intermittent N/V (without obstruction), “significant” weight loss

- **Mild-to-Moderate**
  - Ambulatory, tolerating oral without:
    - Dehydration, toxicity
    - (high fevers, rigors, severe fatigue), abdominal tenderness, painful mass, obstruction, or >10% weight loss
CD Treatment Pyramid

Mild-to-Moderate

- Sulfasalazine
- 5-aminosalicylates
- Antibiotics
- Budesonide EC

Moderate-to-Severe

- Anti-TNF therapies
- 6-MP/Azathioprine
- Methotrexate
- Systemic corticosteroids

Severe-to-Fulminant

- Surgery
- Natalizumab
- Anti-TNF therapies
- Systemic corticosteroids

- Anti-TNF therapies
- 6-MP/Azathioprine
- Methotrexate
- Systemic corticosteroids

- Surgery
- Natalizumab
- Anti-TNF therapies
- Systemic corticosteroids
SASP/Mesalamine Maintenance

• 3 RCT suggested benefit
  – GETAID, Italian IBD, International Mesalamine
    • Many were surgical remitters
• 8 RCT negative
• 5 meta-analyses performed
  – 2 of the early 3 suggested benefit
  – More recently, no clear benefit seen

5-ASA Safety Considerations

• Mesalamine intolerance: Rare but important

• Pancreatitis

• Pneumonitis

• Renal insufficiency

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Antibiotics

• Bacterial flora implicated in pathogenesis
• Metronidazole/ciprofloxacin most studied
• 0.8 to 1 g/d, 10 to 20 mg/kg/d:
  – No benefit in inducing remission over placebo
• Antibiotic maintenance:
  – Long-term abx no data, resistance concerns

Corticosteroids in CD: Induction of Remission

Clinical Remission

% Patients

NCCDS
17 weeks
60%

ECCDS
18 weeks
82%

GETAID
7 weeks
92%

Corticosteroids: Short- and Long-Term Efficacy in Crohn’s Disease

30-day responses (n=74)

- Complete response: 58% (n=43)
- Partial response: 26% (n=19)
- None: 16% (n=12)

1-year responses (n=74) *

- Prolonged response: 28% (n=21)
- Steroid-dependent: 32% (n=24)
- Surgery: 38% (n=28)

*1 patient lost to follow-up

Remission Rates in Acute Crohn’s: Studies with Budesonide CIR

Remission Rates at 8 Weeks (%)

- Bud CIR 9 mg QD
- Bud CIR 4.5 mg BID*
- Placebo BID
- Mesalamine 2 g BID
- Prednisolone 40 mg

*NS vs placebo

Ileum +/- R colon

Budesonide EC
9 mg/d
8 to 16 wks

Budesonide EC
6 mg/d for 6 mo,
Taper off

Isolated colonic
(\textsuperscript{?} ileocolonic)

Metronidazole
10-20 mg/kg
8 to 16 wks

SASP
3 to 6 g/d for
16 weeks

SASP
Mesalazine
Nothing
Summary – Mild Crohn’s Disease

• Mesalamine 3.2 to 4 g po/d
  – Minimally effective vs. placebo
  – Less effective than budesonide/CS
• Sulfasalazine 3 to 6 g/d
• Metronidazole 10 to 20 mg/kg in sulfasalazine non-resp.
• Budesonide EC 9 mg/d in ileal and right colon ds (lower dose for maintenance?)
• Or maybe, no treatment at all for some
Treatment Options for Moderate-to-Severe Crohn’s Disease

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Sequential Therapies for Crohn’s Disease

Disease Severity at Presentation

- Severe
- Moderate
- Mild

Step-Up according to severity at presentation or failure at prior step

Aminosalicylate
Budesonide
Corticosteroid
Anti-TNF

Induction
Maintenance

Natalizumab
Anti-TNF+/-
Thiopurine/MTX

Aminosalicylate
Budesonide/Thiopurine
Corticosteroid
Thiopurine/MTX
Corticosteroid Therapy for Crohn’s Disease

Immediate Outcome* (n = 74)
- Complete Remission: 58% (n = 43)
- Prolonged Response: 32% (n = 24)

1-Year Outcome (n = 74)
- Partial Remission: 26% (n = 19)
- Steroid-Dependent: 28% (n = 21)
- No Response: 16% (n = 12)
- Surgery: 38% (n = 28)

*30 days after initiating corticosteroid therapy.

Budesonide in Active Ileal/Right Colonic Crohn’s Disease


CIR = controlled ileal release. *Mesalamine controlled-release capsules (Pentasa).*

Oral Budesonide:
Efficacy as Maintenance Therapy


Cumulative Probability of Remission

Time (Days)

Efficacy of AZA as Crohn’s Disease Maintenance Therapy After Steroids in Adults*

*Remission induced by prednisolone tapered over 12 wks

Inclusion: Patients were not steroid-dependent

Immunomodulator Therapy for Crohn’s Disease

• Primarily used as steroid-sparing agent or in combination with biologics

• Measure TPMT prior to starting thiopurines
  – AGA Quality Measure
  – Monitor CBC monthly

• 10% to 20% intolerance (nausea) or allergy (pancreatitis)

• Long-term risks of lymphoma (~1/400) & non-melanoma skin cancers

• Methotrexate is alternative to thiopurines
Challenges of Induction To Maintenance: Consider the Population

Steroid-Naïve
Steroid-Induction →
Thiopurine/MTX Maintenance
Anti-TNF Induction →
Thiopurine/MTX Maintenance

Steroid-Dependent
Thiopurine/MTX Maintenance

Failure

Biologic
Challenges of Induction To Maintenance  
Consider the Population (continued)

Steroid-Refractory  
Immunosuppressive naïve  
Anti-TNF induction $\Rightarrow$  
Thiopurine/MTX

Maintenance?  
$\downarrow$

Fail  
Anti-TNF $\pm$ Switch

Steroid-Refractory  
Despite Immunosuppressive  
Anti-TNF induction & Maintenance  
Stop Immunosuppressive

$\downarrow$

Fail  
Switch or Natalizumab
Mucosal Healing and Minimizing Dysplasia and Cancer Risk

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Mayo Score of Endoscopic Severity of Disease
(used in ASCEND, MATRIX, ACT Studies)

0 = NORMAL
- No friability or granularity
- Intact vascular pattern

1 = MILD
- Erythema
- Diminished or absent vascular markings
- Mild granularity

2 = MODERATE
- Marked erythema
- Absent vascular markings
- Granularity
- Bleeds with minimal trauma (friability)
- No ulcerations

3 = SEVERE
- Marked erythema
- Absent vascular markings
- Granularity
- Friability
- Spontaneous bleeding in the lumen
- Ulcerations

Standard “mucosal healing” is subscore of 0 or 1
Achieving “Mucosal Healing” with Therapy in UC

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Trial</th>
<th>Definition of mucosal healing</th>
<th>Evidence of mucosal healing</th>
</tr>
</thead>
</table>
| 5-ASA                          | ASCEND I, II (Asacol) MATRIX (MMX Mesalamine)       | ASCEND I, II: Endoscopic score 0,1  
MATRIX: Complete mucosal healing (a sigmoidoscopy score of 0) | Yes                         |
| Steroids                       |                                                     |                                                                    | No?                         |
| Azathioprine/6-MP               |                                                     |                                                                    | Yes?                        |
| Anti-TNF (UC)                  | ACT 1, 2 (infliximab) ULTRA (adalimumab) PURSUIT-SC (Golimumab) | Mucosal healing was defined as an absolute subscore for endoscopy of 0 or 1. | Yes                         |
| Vedolizumab-Humanized Antibody to the α4β7 integrin | Treatment of UC with a Humanized Antibody to the α4β7 integrin | Modified Baron score of 0 or 1 with no evidence of rectal bleeding | Yes                         |

Fecal Calprotectin Levels in IBD Patients with Active Disease and “Mucosal Healing”

Calprotectin mg/L

Log scale

Mucosal healing

Crohn’s disease
active / remission

Ulcerative colitis
active / remission

* p < 0.0001

Roseth Scand J Gastro 2004
CESAME: Thiopurine Therapy Decreases Incidence of Colorectal Neoplasia in IBD

- French cohort to prospectively determine risk of cancers
  - 19,486 IBD patients (60% CD; 40% UC)
  - At inclusion, 30.1% were receiving thiopurines
  - Follow-up complete in 83.5% of patients

- Observed 36 incident cases of colorectal cancer and 21 cases of high-grade dysplasia
  - Standardized incidence ratio of colorectal cancer was 2.0 (95% CI, 1.4 to 2.7)
  - Male sex, disease duration and extent of colitis identified as significant and independent risk factors

- Trend towards a protective effect of thiopurine therapy (HR: 0.57; 95% CI, 0.24 to 1.32)

Surveillance Guidelines for UC

- Begin surveillance after 8 years for pancolitis; 10 years for left-sided disease
- Every other year or every year after 15 years of disease
- High definition white light or chromoendoscopy
- Start surveillance after diagnosis of PSC
Emerging Therapies

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University of Miami Miller School of Medicine
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SONIC: Corticosteroid-Free Clinical Remission at Week 26

Primary Endpoint

Proportion of Patients (%)

AZA + placebo  IFX + placebo  IFX + AZA

52/170  75/169  96/169

30.6  44.4  56.8

P<0.001  P=0.006  P=0.022

43%

Anti-p40 Mechanism of Action

IL-12

IL-23

Ustekinumab

Briakinumab

IL-12Rβ1

IL-12Rβ2

IL-23R

IL-12Rβ1

NK or T cell membrane

No Signal

Janus Kinase Pathway

- Janus kinase inhibitor
  - Targets a specific intracellular signaling cascade-JAK/STAT pathway
  - The JAK family binds multiple cytokine receptors including:
    - IL2/IL4/IL7/IL9/IL12 (JAK3)
    - IFNs
  - Tofacitinib is JAK3 inhibitor used for psoriasis and rheumatoid arthritis.

TNF, tumor necrosis factor; RA, rheumatoid arthritis

Vedolizumab in UC: Clinical Response, Remission, Mucosal Healing at 6 Weeks

**Clinical Response**
- Placebo: 25.5%
- Vedolizumab: 47.1%
  - Increase: 21.7%
  - 95% CI: 11.6, 31.7%

**Clinical Remission**
- Placebo: 5.4%
- Vedolizumab: 16.9%
  - Increase: 11.5%
  - 95% CI: 4.7, 18.3%

**Mucosal Healing**
- Placebo: 24.8%
- Vedolizumab: 40.9%
  - Increase: 16.1%
  - 95% CI: 6.4, 25.9%

*P* < 0.0001

*P* = 0.0009

*P* = 0.0012

Positioning New and Established Medications for IBD

Induction of Remission/Active Disease
- Cyclosporine
- Vedolizumab
- Ustekinumab (CD)
- Anti-TNFs
- Tofacitinib
- Corticosteroids

Maintenance of Remission
- Vedolizumab
- Anti-TNFs
- MTX
- 6-MP/AZA
- 6-MP/AZA
Case Discussion 1: Ulcerative Colitis
History

• 31-year-old woman
• Has had ulcerative colitis since age 25
• Initial presentation: moderate-to-severe disease
• Initially failed 5-ASA therapy
• Required corticosteroids for induction
• Azathioprine at weight-based (2.5 mg/kg) dosing based with a normal TPMT (thiopurine methyltransferase) phenotype did not control symptoms
History

• Infliximab in combination with azathioprine was attempted.
• Prompt response to infliximab, had been in stable remission on this therapy until recently.
• Over the last 6 months, breakthrough of symptoms would occur between infusions and anticipated a need for her drug.
• Presents now with some urgency, 4 to 6 stools per day, fatigue, and arthralgias.
Management Approach

What is your next step in evaluating this patient with moderate-to-severe ulcerative colitis?

1. Full colonoscopy
2. Stool for: culture, *C difficile* toxin, ova & parasites, WBC count
3. CT of the abdomen
4. Assessment of infliximab trough level and antibodies to infliximab
Management Approach

How would you treat her if the trough levels are zero and antibody titers to infliximab are high?

1. Adalimumab or golimumab
2. Systemic corticosteroids
3. Adalimumab or golimumab in combination with methotrexate
4. Adalimumab or golimumab in combination with azathioprine
Management Approach

How would you treat her if the infliximab level is high (>20 mcg/mL) with no detectable antibodies?

1. Increase the dose and/or decrease interval of infliximab
2. Systemic corticosteroids
3. Surgery
4. Adalimumab or golimumab
5. Adalimumab or golimumab in combination with methotrexate
6. Adalimumab or golimumab in combination with azathioprine
Case Discussion 2: Crohn’s Disease
21-year-old man with a 4-year history of extensive small bowel CD treated with infliximab for the past 3 years presents with increasing cramping abdominal pain, 12-pound weight loss, and diarrhea.

- No recent travel or antibiotics
- No previous abdominal surgery
- SH: Does not smoke
- FH: No FH of IBD
- Meds: infliximab 10 mg/kg q 6 wk
History

- Physical exam shows a well appearing man in NAD with fullness in the RLQ
- Stool samples for enteric pathogens and *C. difficile* negative
- MRE – 5 cm segment of small bowel disease with small bowel dilation proximal to the area of involvement but without inflammation
- IFX level (trough: 9.0 mcg/mL)
- Antibody to infliximab (ATI) negative
- **LABS:**
  - WBC – 8.6 K
  - Hgb – 12
  - Platelet – 334 K
  - CRP – 10.3 (Normal < 4 mg/dL)
What Test Would You Order Next?

1. Colonoscopy
2. Upper GI and small bowel follow through
3. MR enterography
4. CT enterography
5. Capsule endoscopy
Imaging Results

MRE – 5 cm segment of terminal ileal disease with small bowel dilatation proximal to the area of involvement but without inflammation
What Would Be the Best Management Strategy?

1. Increase infliximab
2. Add an antimetabolite (AZA/6MP/MTX) and continue infliximab
3. Switch to adalimumab or certolizumab
4. Switch to natalizumab
5. Continue infliximab and treat for small bowel intestinal overgrowth
6. Send for ileocelecectomy
Follow Up

• Therapeutic infliximab trough level (7 μg/mL) and short segment of fixed non-inflammatory disease
• Sent to surgery and laparoscopic ileocecectomy performed
• Treated postop with metronidazole 500 mg po bid for 3 months as well as azathioprine 2.5 mg/kg
• Doing well 10 months postop with colonoscopy demonstrating 2 isolated aphthous erosions in the neoterminal ileum