Refractory IBD

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- Establish the Correct Diagnosis, Severity of Disease & Extent of Disease
- Evaluate for Disease Complications
- Evaluate for Enteric Infections
- Use Optimal Medication Doses
- Miscellaneous
  - NonAdherence
  - Paradoxical Responses
  - NSAIDs
  - Cigarettes
Refactory IBD

I. Establish the Correct Diagnosis, Severity of Disease & Extent of Disease

- Ulcerative Colitis versus Crohn’s Disease
- Disease Distribution
- Severity of Disease

ACG Guidelines: Determining Severity of Ulcerative Colitis

<table>
<thead>
<tr>
<th>Severity</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>&lt;4 stools/day ± blood</td>
</tr>
<tr>
<td></td>
<td>normal ESR</td>
</tr>
<tr>
<td></td>
<td>no signs of toxicity</td>
</tr>
<tr>
<td>Moderate</td>
<td>≥4 stools/day</td>
</tr>
<tr>
<td></td>
<td>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>

Mayo Score

<table>
<thead>
<tr>
<th>Stool Frequency</th>
<th>Score</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 = Normal</td>
<td>≤2</td>
<td>&lt;2 with no subscore &gt;1</td>
</tr>
<tr>
<td>1 = 1–2 stools/day &gt; normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 = 3–4 stools/day &gt; normal</td>
<td>3–5</td>
<td>Mildly active</td>
</tr>
<tr>
<td>3 ≥5 stools/day &gt; normal</td>
<td>6–9</td>
<td>Moderately active</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Rectal Bleeding</th>
<th>Score</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 = No blood seen</td>
<td>3–5</td>
<td>Mildly active</td>
</tr>
<tr>
<td>1 = Streaks of blood &lt; half the time</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 = Obvious blood with stool most of the time</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 = Blood alone passed</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Findings of Endoscopy</th>
<th>Score</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 = Normal or inactive</td>
<td>6–9</td>
<td>Moderately active</td>
</tr>
<tr>
<td>1 = Mild (erythema, decreased vascular pattern, mild friability)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 = Moderate (marked erythema, absent vascular pattern, friability, erosions)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 = Severe (spontaneous bleeding, ulceration)</td>
<td>10–12</td>
<td>Severely Active</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PGA</th>
<th>Score</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 = Normal</td>
<td>≤2</td>
<td>&lt;2 with no subscore &gt;1</td>
</tr>
<tr>
<td>1 = Mild</td>
<td>3–5</td>
<td>Mildly active</td>
</tr>
<tr>
<td>2 = Moderate</td>
<td>6–9</td>
<td>Moderately active</td>
</tr>
<tr>
<td>3 = Severe</td>
<td>10–12</td>
<td>Severely Active</td>
</tr>
</tbody>
</table>

Colonoscopy Indications

- Suspected Crohn’s or Ulcerative colitis
- Active inflammatory disease vs. fibrostenotic or response to Rx
- Fistulizing disease (including abscess)
- Degree of obstruction (if present)
- Evaluation for Dysplasia or Cancer
- Evaluate for infectious Complications
  - CMV
CT Enterography

- Combines high-resolution CT scanning with some of the concepts of barium radiography
- Ingestion of large volume of a negative contrast agent (either PO or via NJT) to distend loops
  - water or diluted PEG or diluted methylcellulose or highly diluted barium sulfate in sorbitol
- Intravenous contrast, scan after 70 seconds (venous phase)
- Thin slices on helical CT
- Radiation exposure
- More appropriate for advanced disease and complications (abscess, fistula)

CT Enterography Indications - Crohn’s Disease

- Suspected Crohn’s
- Active inflammatory disease vs. fibrostenotic or response to Rx
  - Mural
  - Extra-enteric
- Fistulizing disease (including abscess)
- Degree of obstruction (if present)
- Extra-intestinal findings
Capsule Endoscopy in IBD

- Detects erosions in suspected Crohn’s disease with negative SBFT / colonoscopy
- Need blinded comparison studies vs other imaging to calculate true sensitivity and specificity
- Need to determine specificity (prevalence of SB erosions in general population)
- Need to clarify safety in stricturing Crohn’s disease - patency capsule may help

II. Identify Disease Related Complications

- Fibrostenotic Disease – Inappropriately Treated as Inflammatory Disease
- Intraabdominal Abscesses
- Pelvic Abscesses
- Toxic Megacolon
Identify Disease Related Complications

- Fibrostenotic Disease – Inappropriately Treated as Inflammatory Disease
  - Assess Inflammatory Markers
    - ESR
    - CRP

- CT enterography or MRI enterography
  - Hyperenhancement

Mural Thickening

- Wall thickening > 3mm
- Lumen distended
- Frequently asymmetric
Mural Hyperenhancement

Segmental attenuation greater than adjacent jejenum or ileum (+/- wall thickening)

MRI Enterography: Active Crohn's Disease

T2 and Post-gad images demonstrating marked thickening and enhancement of TI. Note elevated T2 signal within and adjacent to TI (arrows) indicating active disease.
Toxic Megacolon

Disease Complications

- Abdominal / Pelvic Abscess
  - CT abdomen and pelvis with oral and iv contrast
  - MRI pelvis with gadolinium
- Mesenteric Venous Thrombosis
  - CT abdomen and pelvis with oral and iv contrast
  - MRI pelvis with gadolinium
III. Enteric Infections

- Bacterial Infections
  - Aeromonas
  - Salmonella
  - Shigella
  - Yersinia
  - Campylobacter
  - E Coli 0157:H7
    - Shiga Toxin

- CMV

- Clostridium Difficile

- Parasitic Diseases
“Pseudointractibility” of IBD

- Cytomegalovirus (CMV)
  - 50-80% of the world’s population is seropositive
  - Initial infection in the immune competent host is typically mild – goes undetected clinically
  - Chronic latent state follows- virus remains present within host cells. Virus proliferation is prevented by host cell-mediated immunity.
  - When immune containment fails-reactivation with viral proliferation and severe systemic illness may ensue.

“Pseudointractibility” of IBD

- Cytomegalovirus (CMV)
  - Systemic CMV manifestations
    - Fever, pancytopenia, inflammatory changes of multiple organs- including liver, lungs, retina, colon.
  - Patients are rendered susceptible to systemic CMV by
    - Treatment with immunosuppressive medications or
    - Illnesses that reduce cell mediated immunity (e.g. HIV)
  - Patients with IBD get CMV in the presence of colonic inflammation and ongoing immunosuppressive therapy.
“Pseudointractibility” of IBD

• Cytomegalovirus (CMV)
  • + CMV IgG
    • A person was infected with CMV at some time during their life (uncertain exactly when).
    • If antibody tests are paired acute- and convalescent – phase serum samples show a fourfold rise in IgG CMV Ab and CMV IgM antibody is present or CMV virus is cultured from a urine or throat specimen – active CMV is present.

Clostridium Difficile in IBD

• Increasing prevalence in out-patient and hospitalized patients
• Present in 16% of all hospitalized IBD pts.
• 76% of infected hospitalized pts. acquired Clostridium difficile as outpatients.
• 40% had NO antibiotic exposure

Issa, et al. CGH 2007
Clostridium Difficile in IBD
Diagnostic Testing

- Endoscopy
  - pseudomembranous colitis
- Culture
- Cell culture cytotoxin test
- Enzyme immunoassay (EIA) toxin test
- PCR toxin gene detection

<table>
<thead>
<tr>
<th>Method</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enzyme Immunoassays</td>
<td>33-97</td>
<td>83-100</td>
</tr>
<tr>
<td>Cell culture neutralization</td>
<td>65-80</td>
<td>97-98</td>
</tr>
<tr>
<td>Glutamate dehydrogenase* paired with toxin testing (2-step algorithm)</td>
<td>80-98</td>
<td>96-98</td>
</tr>
<tr>
<td>Anaerobic toxigenic culture</td>
<td>&gt;90</td>
<td>96-97</td>
</tr>
<tr>
<td>Nucleic acid amplification</td>
<td>88-96</td>
<td>94-100</td>
</tr>
</tbody>
</table>
“Pseudointractibility” of IBD

- CMV
- Clostridium Difficile
- NSAIDs
- Cigarette
  - Cessation in UC
  - Use in CD

IV. Use of Optimal Medication Doses
# Mesalamine Comparative Doses

## Mild to Moderate UC

<table>
<thead>
<tr>
<th></th>
<th>Recommended Treatment Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfasalazine</td>
<td>4-6 grams</td>
</tr>
<tr>
<td>Mesalamine</td>
<td></td>
</tr>
<tr>
<td>- MMX mesalamine</td>
<td>2.4-4.8 grams</td>
</tr>
<tr>
<td>- Delayed Release</td>
<td>2.4-4.8 grams</td>
</tr>
<tr>
<td>- Controlled Release</td>
<td>4.0 grams daily</td>
</tr>
<tr>
<td>- Mesalamine Granules*</td>
<td>3.0 grams daily</td>
</tr>
<tr>
<td>Balsalazide</td>
<td>6.75 grams</td>
</tr>
</tbody>
</table>

* - Not approved for induction

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### Use adequate dose

- May take 2-4 weeks to exert their effects
- If there are still active symptoms on maximal doses of oral mesalamine, the addition of topical therapy in the form of a nightly mesalamine enema or suppository should be considered in UC patient.
## Mesalamine in Ulcerative Colitis
### Median Time to Symptom Resolution

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose / Time</th>
<th>Dose / Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesalamine Granules</td>
<td>1.0 grams tid</td>
<td>3.0 grams QD</td>
</tr>
<tr>
<td></td>
<td>16 days (a)</td>
<td>12 days (A)</td>
</tr>
<tr>
<td>Delayed Release Mesalamine</td>
<td>4.8 grams daily</td>
<td>4.8 grams daily</td>
</tr>
<tr>
<td>Rectal Bleeding</td>
<td>9 days</td>
<td>Stool Frequency</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 days</td>
</tr>
<tr>
<td>MMX Mesalamine</td>
<td>2.4 grams daily</td>
<td>4.8 grams daily</td>
</tr>
<tr>
<td></td>
<td>7 days b</td>
<td>8 days b</td>
</tr>
<tr>
<td></td>
<td>19 days c</td>
<td>20 days c</td>
</tr>
</tbody>
</table>


A - Resolution of symptoms defined as ≤3 stools/day and free of blood.
B - Median time to resolution of rectal bleeding
C - Median time to normalization of stool frequency

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### Meta-Analysis: Randomized Clinical Trials Evaluating AZA and 6-MP* for the Induction of Clinical Remission of UC

- Medication may take 2-6 months to see effect
- AZA: 2.5 mg/kg
- 6-MP: 1.5 mg/kg

*AZA and 6-MP are not approved for UC

Infliximab in Ulcerative Colitis: ACT 1 and ACT 2 Study Design

- Active UC: Mayo score $\geq 6$; baseline mean = 8
- Endoscopic score of $\geq 2$
- No crossover arm
- Includes steroid-refractory patients (40 mg PO x 2 weeks or IV for 1 week): $\sim 30\%$ in each group

Endpoints
- Response: $\geq \downarrow$ Mayo score by 30\% and 3 points
- Remission: Mayo $< 2$


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Infliximab in Ulcerative Colitis: ACT 1 and ACT 2 Study

- Although not studied in a controlled manner in these trials some patients with an initial response to 5 mg/kg in whom the benefit is attenuated after multiple doses may benefit from
  - Dose escalation
  - Shortening dose intervals
  - Or both
- Similar response and remission rates whether steroid refractory or naïve

Infliximab in Ulcerative Colitis: ACT 1 and ACT 2 Study

- The success of a steroid free remission at week 54 occurs in 21% of patients.
- These studies did not prospectively address whether concomitant thiopurine therapy would influence clinical success rate.


Management of Severe Ulcerative Colitis

Severe Disease

- Despite optimal dose of
  - Steroids orally (40-60 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
A Placebo Controlled, Double Blind, Randomized Trial of Intravenous Cyclosporine in Severe, Steroid-Refractory Ulcerative Colitis

Placebo

- 9
  - Failed; went to surgery

Cyclosporine (CSA)

- 20
  - Failed; went to surgery
  - Crossover to Open label IV CSA
  -成功

- 11
  - Success
  - Failed; went to surgery

Initial successes 9/11 - 82% (P<0.001)
Total successes 14/18 - 88%
Mean response time – 7 days (3-14 days)


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RCTs of Severe Ulcerative Colitis:
Acute Response to CSA

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>20</td>
<td>30</td>
<td>30</td>
<td>73</td>
</tr>
<tr>
<td>CyA dose mg/kg/day</td>
<td>4 (11)</td>
<td>4 (15)</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Control (n)</td>
<td>Placebo (9)</td>
<td>IV Steroids</td>
<td>CYA/IV steroids</td>
<td>CYA 2mg/kg/day</td>
</tr>
<tr>
<td>Duration</td>
<td>14 days</td>
<td>8 days</td>
<td>14 days</td>
<td>8 days</td>
</tr>
<tr>
<td>+ response (n)</td>
<td>9/11</td>
<td>9/14</td>
<td>10/15</td>
<td>32/38</td>
</tr>
<tr>
<td>CyA Control</td>
<td>0/9</td>
<td>8/15</td>
<td>14/15</td>
<td>30/35</td>
</tr>
<tr>
<td>CyA mean blood concentration</td>
<td>482 ng/ml</td>
<td>376 +/- 22 ng/ml</td>
<td>NR</td>
<td>332 ng/ml</td>
</tr>
</tbody>
</table>
Infliximab for Moderate or Severe Refractory UC

<table>
<thead>
<tr>
<th>% of Patients Achieving Endpoint</th>
<th>ACT 1(^1) (N=364)</th>
<th>ACT 2(^2) (N=364)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Infliximab</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 mg/kg</td>
</tr>
<tr>
<td>Clinical response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 week</td>
<td>37.2</td>
<td>69.4(^*)</td>
</tr>
<tr>
<td>30 week</td>
<td>29.8</td>
<td>52.1(^*)</td>
</tr>
<tr>
<td>Clinical remission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 week</td>
<td>14.9</td>
<td>38.8(^*)</td>
</tr>
<tr>
<td>30 week</td>
<td>15.7</td>
<td>33.9(^*)</td>
</tr>
<tr>
<td>Mucosal healing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 week</td>
<td>33.9</td>
<td>62.0(^*)</td>
</tr>
<tr>
<td>30 week</td>
<td>24.8</td>
<td>50.4(^*)</td>
</tr>
<tr>
<td>Discontinued steroids (30 week)</td>
<td>10.1</td>
<td>21.7(^*)</td>
</tr>
</tbody>
</table>

\(^*\) P < 0.001 vs. placebo; \(^*\) P < 0.005 vs. placebo; \(\dagger\) P = 0.009 vs. placebo.


Infliximab for Severe Ulcerative Colitis: Avoidance of Colectomy: Controlled trial

- Randomized, double blind, placebo controlled trial
- Patients failing IV steroids with:
  - Fulminant disease at day 4, or
  - Severe disease at day 6-8
- Treated with:
  - single infusion 5mg/kg infliximab (N= 24) or
  - placebo (n=21)
- Clinical Endpoint at Day 90
  - The avoidance of death or colectomy

Infliximab for Severe Ulcerative Colitis

- **Colectomy in**
  - 29% of all infliximab patients
  - 67% of placebo patients (p= 0.017)

- **Colectomy in fulminant patients**
  - Infliximab treated: 47% (7/15) (p=0.30)
  - Placebo treated: 69% (9/13)

- **Secondary Endpoints: Clinical & Endoscopic Remission**
  - Placebo: 33%
  - Infliximab: 40%


Infliximab, Azathioprine, or Infliximab + Azathioprine for Treatment of Moderate to Severe Ulcerative Colitis: The UC Success Trial

- **Objective**
  - To assess the best treatment strategy in patients with moderate-severe UC who are failing corticosteroids

- **Patients (N=231)**
  - Severe UC (Mayo score ≥6)
  - Failing corticosteroids
  - Naïve to azathioprine or had stopped ≥3 months prior to entry

- **Treatments**
  - AZA 2.5 mg/kg + placebo
  - IFX 5 mg/kg + placebo
  - IFX 5 mg/kg + AZA 2.5 mg/kg
  - At week 8, nonresponders in the AZA arm were eligible for IFX 5 mg/kg at weeks 8, 10, and 14

- **Primary end point**
  - Steroid-free remission at week 16 (total Mayo score ≤2)

Ulcerative Colitis: Success Trial

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>Steroid-free remission</th>
<th>Response</th>
<th>Mucosal Healing</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFX+AZA (n=78)</td>
<td>40</td>
<td>22</td>
<td>24</td>
</tr>
<tr>
<td>IFX (n=77)</td>
<td>69</td>
<td>50</td>
<td>37</td>
</tr>
<tr>
<td>AZA (n=66)</td>
<td>77</td>
<td>63</td>
<td>55</td>
</tr>
</tbody>
</table>

* P < 0.05 compared to IFX;  *
# P < 0.05 compared to AZA


Tacrolimus for Severely Active Ulcerative Colitis

- 63 hospitalized patients with moderately to severely active UC (steroid-dependent or steroid-refractory)
- Stable doses of 5ASA
- Randomized to 14 days of treatment with:
  - Oral tacrolimus (high dose; trough level 10-15 ng/mL)
  - Oral tacrolimus (low dose; trough level 5-10 ng/mL)
  - Placebo
- Disease activity measured with Mayo Score
- Primary endpoint
  - Percentage improvement (complete response [Mayo score = 0] or partial response [↓ in Mayo Score ≥ 4] at Day 14

NNT= 2

Tacrolimus for Severely Active Ulcerative Colitis

- **Secondary endpoints**
  - % clinical remission (Mayo Score ≤2) at Day 14
  - % mucosal healing (decrease in endoscopy subscore from 2-3 at baseline to 0-1 at Day 14)

- **Nephrotoxicity**
  - 5% in high-dose group
  - 5% in low-dose group
  - 0% in placebo group

![Graph showing clinical remission and mucosal healing](image)


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When to Introduce Anti-TNF Therapy

I. **Crohn's Disease (CD)**
   - Steroid Dependent CD
   - Steroid Refractory CD
   - Immunomodulator Refractory or Intolerant CD
   - Complex Fistulizing CD
   - Prevention of Postoperative recurrence?
   - Clinical predictors of a poor outcome at diagnosis?

II. **Ulcerative Colitis (UC)**
   - Steroid Refractory UC
   - Steroid Dependent UC
   - Immunomodulator Refractory or Intolerant UC
   - Clinical predictors of a poor outcome at diagnosis?
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

Secondary Nonresponder

**Switch from Infliximab to Adalimumab**

- GAIN trial, 325 adults 18-75 years of age with moderate to severe Crohn disease (CDAI score, 220-450 points) and who had lost response to infliximab or had adverse events were randomly assigned to receive induction doses of adalimumab, 160 mg/80 mg, or placebo at weeks 0 and 2; 301 completers
- Twenty-one percent (34 of 159) of patients in the adalimumab group vs 7% (12 of 166) in placebo group achieved remission at week 4
- 70-point response at week 4 in 52% (82 of 159) of patients in adalimumab group vs 34% (56 of 166) of patients in placebo group

GAIN: Clinical Response and Remission with Adalimumab

In Patients with Moderate to Severe CD and Secondary Failure to Infliximab

<table>
<thead>
<tr>
<th>Patients, %</th>
<th>Placebo</th>
<th>Adalimumab 160/80 mg EOW, SC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response (CR70)</td>
<td>34/166</td>
<td>52/159</td>
</tr>
<tr>
<td>Response (CR100)</td>
<td>24/166</td>
<td>38/159</td>
</tr>
<tr>
<td>Remission CDAI ≤150</td>
<td>7/166</td>
<td>21/159</td>
</tr>
</tbody>
</table>

***p<0.001, **p<0.01, both vs placebo
Full analysis population

Secondary Nonresponder: Switching from Infliximab to Certolizumab

- WELCOME: 26 week study; 539 patients with active Crohn's disease and secondary failure to infliximab received open-label induction with subcutaneous certolizumab 400 mg at weeks 0, 2, and 4
- Responders were then randomized to certolizumab 400 mg every 2 or every 4 weeks through week 24
- The primary end point was response at week 6
- Secondary end points included remission at week 6 and response and remission at week 26

Secondary Nonresponder: Switching from Infliximab to Certolizumab

- At week 6, 334 of 539 patients (62.0%) achieved response and 212 of 539 (39.3%) achieved remission.
- A total of 329 patients were randomized and received maintenance therapy.
  - At week 26, 39.9% (67 of 168) and 36.6% (59 of 161) of patients in the every 4 weeks and every 2 weeks groups were in clinical response, respectively (P = .55).
  - Corresponding remission rates at week 26 were 29.2% and 30.4%, respectively (P = .81).

Certolizumab in Patients with Moderate to Severe CD and Secondary Failure to Infliximab

Response and Remission Rates

(A) over the open-label induction phase (n = 539)

(B) at week 26 (n = 329)

Secondary Nonresponder
Switching to a Third Anti-TNF

• Open label study of the use of certolizumab or adalimumab after failure and/or intolerance to two different anti-TNF agents
• Sixty-seven patients treated with certolizumab (n = 40) or adalimumab (n = 27) were included
  – Clinical response observed in 41 patients (61%) at week 6 and 34 patients (51%) at week 20
  – Probability of remaining on treatment at 3, 6 and 9 months was 68%, 60% and 45%, respectively
  – At end of follow-up, third anti-TNF stopped in 36 patients for intolerance (n = 13), or failure (n = 23)
  – Two deaths observed (sudden death and line sepsis)


V. 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

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

1st agent = adalimumab or certolizumab pegol
- ATI Low
  - Adequate serum infliximab
  - Switch to 2nd anti-TNF
  - OR Switch to agent from a different class

Don’t Forget:
- NonAdherence
- Paradoxical Responses
- NSAIDs
- Cigarettes
Conclusion

- Assess disease extent, severity, type of IBD
- Assess for complications
  - Stricture, Abscess, Fistula, Thrombosis
- Exclude enteric Infections
- Optimize medical therapy
- Beware of drug intolerances and paradoxical side effects
- Assess adherence
- Consider surgery when appropriate.