What to Do When Conventional IBD Therapy Fails

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FDA-approved biologics for IBD

**Crohn’s Disease**
- Anti-TNF antibodies
  - Adalimumab (Humira®)
  - Certolizumab pegol (Cimzia®)
  - Infliximab (Remicade®)
- Selective adhesion molecule
  - Natalizumab (Tysabri®)
  - Vedolizumab (Entyvio®)

**Ulcerative Colitis**
- Anti-TNF antibodies
  - Adalimumab (Humira®)
  - Infliximab (Remicade®)
  - Golimumab (Simponi®)
- Selective adhesion molecule
  - Vedolizumab (Entyvio®)
28 yo with Refractory Disease

- 28 yo male comes to office for 2\textsuperscript{nd} opinion with 3 year history of Crohn’s ileocolitis.

- He has abdominal pain and diarrhea (10-12x / day) with urgency and 10\# wt loss. He has been on 2.5 mg /kg/day of azathioprine and 4 grams of mesalamine for over a year

- He is a non-smoker

- No previous h/o surgery
28 yo with Refractory Disease (Part B)

• On exam he looks thin, afebrile. Tender to palpation in RLQ. HR is 100
  – Labs: WBC= 10k, Hgb 11, Plt 600, CRP 20
  – Stool studies negative
28 yo with Refractory Disease (Part C)

- Started on Infliximab and receives the induction sequence of 5 mg/kg at weeks 0, 2 and 6 without improvement.
  - Has lost another 5# and is still having more than 10 stools per day

- Colonoscopy 10 wks after starting IFX.

- **CTE:** 8 cm segment in distal ileum with inflammation but no stricture
What Do You Do Now?

• Options
  – Double next Infliximab dose
  – Switch to another anti-TNF
  – Switch to vedolizumab or natalizumab
  – Send for Surgery
  – Punt
Approach to Refractory Patients

1\textsuperscript{st} rule out other causes for symptoms

- IBS
  - Pt colonoscopy confirmed active disease
- Bile Salt diarrhea
  - No history of resection and active disease on scope
- Fibrotic stricture
  - None seen on imaging or scope
- Infection - especially C.diff
  - Stool studies are negative
Complications: *Clostridium difficile* Infected Patients With IBD

**Hospitalizations**

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998</td>
<td>0</td>
</tr>
<tr>
<td>1999</td>
<td>0</td>
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<tr>
<td>2000</td>
<td>2</td>
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<td>2001</td>
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<td>2002</td>
<td>10</td>
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<tr>
<td>2003</td>
<td>10</td>
</tr>
<tr>
<td>2004</td>
<td>25</td>
</tr>
<tr>
<td>2005</td>
<td>30</td>
</tr>
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</table>

**Colectomies**

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td># of Patients With IBD With C. diff: 10, # of Colectomies: 1</td>
</tr>
<tr>
<td>2005</td>
<td># of Patients With IBD With C. diff: 5, # of Colectomies: 45</td>
</tr>
</tbody>
</table>

Approach to Refractory Patients

2nd - Make Sure Current Meds Optimized

• Check metabolites

• Check anti-TNF levels
6-TG Levels and Clinical Response

Dubinsky et al, *Gastroenterology* 2000
SONIC: Clinical Remission Without Corticosteroids

By Trough IFX Concentration at Week 26

IFX Concentration (mg/ml) at Week 30

Clinical Utility of Measuring Infliximab and HACA Levels in Patients with IBD

Clinical Outcomes in Patients with Detectable HACA (N=35)*

- Complete/Partial Response (%)
  - Anti-TNF Changed (11/12)
  - Infliximab Increased (1/6)
  - P<0.004

Clinical Outcomes in Patients with Subtherapeutic Concentrations (N=69)*

- Complete/Partial Response (%)
  - Anti-TNF Changed (2/6)
  - Infliximab Increased (25/29)
  - P<0.016

ADA Levels and Anti-Adalimumab Antibodies (ATA) and Outcomes

• 66 patients: 27% with detectable ATA
  – 59 (89%) CD, 7 (11%) UC

• ADA level ≥ 5 µg/ml is associated with lower CRP

• Conclusions:
  – ADA level ≥5 µg/mL correlates with lower CRP and mucosal healing;

Proportion of Patients Achieving Clinical Remission by Serum IFX Concentration: ACT 1 and 2

At wks 8, 30 and 54, the proportion of patients achieving clinical remission increased with increasing quartiles of IFX concentrations.

<table>
<thead>
<tr>
<th>IFX Conc. (% patients)</th>
<th>1st Quartile</th>
<th>2nd Quartile</th>
<th>3rd Quartile</th>
<th>4th Quartile</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 8</td>
<td>26.3% (&lt;21.3μg/mL)</td>
<td>37.9% (≥21.3-&lt;33μg/mL)</td>
<td>43.9% (≥33-&lt;47.9μg/mL)</td>
<td>43.1% (&gt;47.9μg/mL)</td>
<td>P=0.0504</td>
</tr>
<tr>
<td>Week 30</td>
<td>14.6% (&lt;0.11μg/mL)</td>
<td>25.5% (≥0.11-&lt;2.4μg/mL)</td>
<td>59.6% (≥2.4-&lt;6.8μg/mL)</td>
<td>52.1% (&gt;6.8μg/mL)</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>Week 54</td>
<td>21.1% (&lt;1.4μg/mL)</td>
<td>55.0% (≥1.4-&lt;3.6μg/mL)</td>
<td>79.0% (≥3.6-&lt;8.1μg/mL)</td>
<td>60.0% (&gt;8.1μg/mL)</td>
<td>P=0.0066</td>
</tr>
</tbody>
</table>
Higher Serum Infliximab Concentration is Associated with Longer Remission and Better Endoscopy Score in Patients with Crohn’s Disease

- **Study design:** prospective cohort in moderate-severe CD
- **N=105**
- **Median follow-up:** 88 weeks
- **Efficacy**
  - Infliximab concentrations were positively correlated with the interval of clinical remission and change in endoscopic score

Relation of clinical outcomes to serum infliximab (N = 105). (A) Duration of interval clinical remission defined as the percentage of time (weeks) between infusions with HBI score of 2 or less. (B) Serum CRP. (C) Endoscopic improvement defined as the percentage change in endoscopic score from the baseline to the follow-up evaluation. (●) Patients who discontinued infliximab before 52 weeks. (○) Patients who continued infliximab beyond 52 weeks.

Higher trough levels of adalimumab are associated with higher rates of mucosal healing.

## Factors Affecting the Pharmacokinetics of Monoclonal Antibodies

<table>
<thead>
<tr>
<th>Factor</th>
<th>Impact on Pharmacokinetics</th>
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<tbody>
<tr>
<td>Presence of ADAs</td>
<td>• Decreases serum mAbs</td>
</tr>
<tr>
<td></td>
<td>• Threefold-increased clearance</td>
</tr>
<tr>
<td></td>
<td>• Worse clinical outcomes</td>
</tr>
<tr>
<td>Concomitant use of IS</td>
<td>• Reduces formation</td>
</tr>
<tr>
<td></td>
<td>• Increases serum mAbs</td>
</tr>
<tr>
<td></td>
<td>• Decreases mAb clearance</td>
</tr>
<tr>
<td></td>
<td>• Better clinical outcomes</td>
</tr>
<tr>
<td>High baseline TNF-α</td>
<td>• May decrease mAbs by increasing clearance</td>
</tr>
<tr>
<td>Low albumin</td>
<td>• Increases clearance</td>
</tr>
<tr>
<td></td>
<td>• Worse clinical outcomes</td>
</tr>
<tr>
<td>High baseline CRP</td>
<td>• Increases clearance</td>
</tr>
<tr>
<td>Body size</td>
<td>• High BMI may increase clearance</td>
</tr>
<tr>
<td>Gender</td>
<td>• Males have higher clearance</td>
</tr>
</tbody>
</table>

mAB, monoclonal antibody; ADA, antidrug antibody
IFX in stool

A. Week 2 clinical response (n = 30)

B. Week 8 endoscopic response (n = 21)

C. 3 months clinical response (n = 30)

Brandse et al. Gastro 2015
Concentration of IFX and ATI Levels Before and After Immunomodulator Treatment

Approach to Refractory Patients

2nd - Make Sure Current Meds Optimized

• Check metabolites
  – 6-TG = 280 / 6-mmp = 5750

• Check anti-TNF levels
  – Trough levels 10 mg / ml
  – no ATIs
Approach to Refractory Patients

3rd – is MOA effective?

• Is this a secondary loss of response?
• Is patient truly primary TNF non-responder?
  – If so then use a agent with different MOA
    • Vedolizumab or Natalizumab
Definition of non-Response to Rx

• Primary Nonresponders
  – Individuals who fail to respond to initial induction therapy within 12 weeks
  • Approximately 35-40% of patients in anti-TNF clinical trials are primary nonresponders

• Secondary Nonresponders
  – Improve after initial induction but subsequently lose their response or become intolerant of their anti-TNF agent
Switching to Another TNF

Adalimumab for IFX Failures at Wk 4

Certolizumab pegol for IFX Failures at Wk 6 (open label)

2- Sandborn, Clin Gastro Hep 2010
Selective Adhesion Molecules
Vedolizumab for UC (Induction week 6)

Vedolizumab for UC (Wk 52)

Vedolizumab for CD

A Induction (week 6)

- Placebo (N=148) vs Vedolizumab (N=220)
  - Clinical Remission: 6.8% vs 14.5%, P=0.02
  - CDAI-100 Response: 25.7% vs 31.4%, P=0.23

- Placebo (N=153)
  - Clinical Remission: 21.6%
  - CDAI-100 Response: 30.1%
  - Glucocorticoid-Free Remission: 15.9%
  - Durable Clinical Remission: 14.4%

- Vedolizumab, every 8 wk (N=154)
  - Clinical Remission: 39.0%
  - CDAI-100 Response: 43.5%
  - Glucocorticoid-Free Remission: 31.7%
  - Durable Clinical Remission: 21.4%

- Vedolizumab, every 4 wk (N=154)
  - Clinical Remission: 36.4%
  - CDAI-100 Response: 45.5%
  - Glucocorticoid-Free Remission: 28.8%
  - Durable Clinical Remission: 16.2%

P-values:
- Placebo vs Vedolizumab, every 8 wk: P<0.001, P=0.01, P=0.02
- Placebo vs Vedolizumab, every 4 wk: P=0.004, P=0.005, P=0.04

Approach to Refractory Patients –

4th – Does the Patient Need an agent with Novel MOA?

- Is the patient a candidate for a trial?

- What are some of the non-FDA approved Options we have some data on?
  - Ustekinumab
  - IVIG
  - Other?
## IVIG for Refractory IBD

24 patients analyzed (23 with Cd, 1 with UC)

<table>
<thead>
<tr>
<th>Failure of Standard Treatment</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td></td>
</tr>
<tr>
<td>Histoplasmosis</td>
<td>2</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>1</td>
</tr>
<tr>
<td>Pulmonary fungal infections</td>
<td>2</td>
</tr>
<tr>
<td>Recurrent C.Diff &amp; history of breast ca</td>
<td>1</td>
</tr>
</tbody>
</table>
IVIG for Refractory IBD

- IVIG dose: 0.4 g/kg/day X 3 days, then 0.4g/kg once monthly

- With a partial response or lost response – dose increased to 0.4g/kg every 2 weeks
Ustekinumab in CD - Background
Ustekinumab in CD - Background

**IL-12 and IL-23**

This is a human monoclonal antibody to the p40 sub-unit of IL-12 /23. IL-12 and 23 are produced by macrophages and dendritic cells.

**IL-12**
- p40
- p35
- anti p40 (CNT01275)
- anti p35

**IL-23**
- p40
- p19
- anti p19

IL-12Rβ1  IL-12Rβ2  IL-23R  IL-12Rβ1

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Ustekinumab
- IgG$_{1k}$ monoclonal antibody
- Blocks the biologic activity of IL-12 and IL-23 through p40 subunit
- Advantageous for anti-TNF non-responders

**CERTIFI Trial**

### Induction

<table>
<thead>
<tr>
<th>Group</th>
<th>Week 8 Response</th>
<th>Week 8 Remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>17.4</td>
<td>10.6</td>
</tr>
<tr>
<td>Ustekinumab 1 mg/kg</td>
<td>32.1</td>
<td>17.6</td>
</tr>
<tr>
<td>Ustekinumab 3 mg/kg</td>
<td>131.8</td>
<td>618.2</td>
</tr>
<tr>
<td>Ustekinumab 6 mg/kg</td>
<td>43.5</td>
<td>18.3</td>
</tr>
</tbody>
</table>

### Maintenance

<table>
<thead>
<tr>
<th>Group</th>
<th>Week 22 Maintenance Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo Response</td>
<td>42.5</td>
</tr>
<tr>
<td>Placebo Remission</td>
<td>27.4</td>
</tr>
<tr>
<td>Ustekinumab Remission</td>
<td>69.4</td>
</tr>
<tr>
<td>Ustekinumab Response</td>
<td>41.7</td>
</tr>
</tbody>
</table>

Ustekinumab – UNITI Trials

Uniti 1

- Response at Week 6 (%)
- Placebo (n=247)
- 130 mg (n=245)
- ~6 mg/kg (n=249)

- 21.5
- 34.3
- 33.7

- P=.002
- P=.003

Uniti 2

- Patients, %
- Placebo
- 130 mg
- ~6 mg/kg
- Combined

- 28.7
- 51.7
- 55.5
- 53.6

- n=209
- n=209
- n=209
- n=418

- P<0.001

Ustekinumab for Refractory CD

- N= 45 pts
  - 100 % failed at least 1 TNF
  - 73% had prior surgery

- Dosed with novel SQ dosing schedule
  - 90mg at weeks 0, 4, with a 270mg booster dose at week 8 if no or limited response.
  - The maintenance dose used was 90 mg every 8 weeks.

Harris K, Schwartz DA, ACG 2014
Ustekinumab for Refractory CD

- 57% in Remission (33)
- 43% No Response

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JAK Inhibitor – Background
JAK Inhibitor – Background

JAK3/γc inhibitors will block signalling by six cytokines

Receptors signalling through JAK3
- IL-2
- IL-4
- IL-7
- IL-9
- IL-15
- IL-21
## Tofacitinib (JAK3 inhibitor) in UC- OCTAVE Results

<table>
<thead>
<tr>
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<th>OCTAVE Induction 1</th>
<th>OCTAVE Induction 2</th>
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<tbody>
<tr>
<td></td>
<td>Tofacitinib 10 mg BID</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>N=476</td>
<td>N=122</td>
</tr>
<tr>
<td><strong>TNFi-treated</strong></td>
<td>32/254 (12.6)</td>
<td>1/65 (1.5)</td>
</tr>
<tr>
<td><strong>TNFi-naïve</strong></td>
<td>56/222 (25.2)</td>
<td>9/57 (15.8)</td>
</tr>
<tr>
<td><strong>Mucosal healing at Week 8, n (%)</strong></td>
<td>149 (31.3)***</td>
<td>19 (15.6)</td>
</tr>
<tr>
<td><strong>TNFi-treated</strong></td>
<td>61/254 (24.0)</td>
<td>4/65 (6.2)</td>
</tr>
<tr>
<td><strong>TNFi-naïve</strong></td>
<td>88/222 (39.6)</td>
<td>15/57 (26.3)</td>
</tr>
</tbody>
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Vanderbilt Digestive Disease Center

## Tofacitinib (JAK3 inhibitor) in CD- Results

<table>
<thead>
<tr>
<th></th>
<th>Placebo N=90</th>
<th>Tofacitinib 5 mg BID N=85</th>
<th>Tofacitinib 10 mg BID N=86</th>
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<tbody>
<tr>
<td>Remission at Week 8, NRI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (%) (^1)</td>
<td>33 (36.7)</td>
<td>37 (43.5)</td>
<td>37 (43.0)</td>
</tr>
<tr>
<td>Remission at Week 8 in TNF-experienced patients, NRI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (%) (^1)</td>
<td>25 (36.2)</td>
<td>26 (38.2)</td>
<td>28 (42.4)</td>
</tr>
<tr>
<td>Response 100 at Week 8, NRI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (%) (^1)</td>
<td>49 (54.4)</td>
<td>60 (70.6)*</td>
<td>59 (68.6)</td>
</tr>
</tbody>
</table>

\(^1\) Data presented as n (%)
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

1st agent = adalimumab or certolizumab pegol

ATI Low
- Adequate serum infliximab

ATI High
- Adequate serum infliximab
  - Switch to 2nd anti-TNF
  - OR
    - Switch to agent from a different class

Inflammation present
- No complication

Symptomatic therapy for presumed irritable bowel-like symptoms

Inflammation absent
- No complication

Specific treatment for complication

IBD Working Group (ibdwg.org)
Case Study Conclusion

- Patient switch to Vedolizumab
  - Continued on azathioprine

- Improved over next 10 weeks and continued on maintenance q 8 week infusions
Thank you for your time!