Moderate to Severe CD and UC Treatment Options in 2017

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Moderate to Severe IBD

**Pre-2017**

- Sequential step up therapy
- Assess & treat current IBD disease **activity**
- Standardized Induction and Maintenance tx
- Periodic standard labs
- **Reactive** IBD management

**2017 and beyond**

- Early intervention therapy
- Assess and treat IBD **activity severity**
- Individualized Induction and Maintenance tx
- Therapeutic drug monitoring (TDM)
- **Proactive** IBD Management
Treat to Target- What is the Target?

- Symptom improvement/resolution is not enough
- Colonoscopic tissue healing
- Biomarker normalization
- Histologic normalization
- DEEP REMISSION

Risk of IBD Progression

<table>
<thead>
<tr>
<th>Low Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Localized Anatomic extent</td>
<td>• Extensive disease (colitis or ileocolitis)</td>
</tr>
<tr>
<td>• Mild endoscopic disease</td>
<td>• Deep Ulcers</td>
</tr>
<tr>
<td></td>
<td>• Fistula or abscess for CD</td>
</tr>
<tr>
<td></td>
<td>• Age &lt;40</td>
</tr>
<tr>
<td></td>
<td>• High CRP and ESR</td>
</tr>
<tr>
<td></td>
<td>• HX of Requiring Steroids</td>
</tr>
<tr>
<td></td>
<td>• History of hospitalization or surgery</td>
</tr>
<tr>
<td></td>
<td>• C. difficile infection</td>
</tr>
<tr>
<td></td>
<td>• CMV Infection</td>
</tr>
</tbody>
</table>
Low Risk vs High Risk

Low Risk

High Risk

- Surgery
- Anti-integrin
- Anti-TNF
- Anti-IL12/23 inhibitor
- Cyclosporine

Immunosuppressant

Corticosteroid

5-ASA

Ulcerative Colitis

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminosalicylates (ASA to mesalamine)</td>
<td>oral therapy (diazo bond, pH, controlled release)</td>
</tr>
<tr>
<td></td>
<td>topical rectal therapy (mesalamine suppository and enema)</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>systemic-oral, IV (prednisone)</td>
</tr>
<tr>
<td></td>
<td>non-systemic-topical po/rectal (budesonide MMX, Budesonide foam)</td>
</tr>
<tr>
<td>Immunomodulators</td>
<td>thiopurine (AZA, 6MP)</td>
</tr>
<tr>
<td></td>
<td>Mtx (?)</td>
</tr>
<tr>
<td>Biologic</td>
<td>Anti-cytokine: Anti-TNF(IFX, ADA, GOL)</td>
</tr>
<tr>
<td></td>
<td>Anti-integrin (VEDO)</td>
</tr>
<tr>
<td>Small Molecules</td>
<td>Anti S1P1 inhibitor (Ozanimod)</td>
</tr>
<tr>
<td></td>
<td>JAK inhibitor (tofacitinib)</td>
</tr>
</tbody>
</table>

Crohn's disease

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminosalicylates (?)</td>
<td></td>
</tr>
<tr>
<td>Corticosteroid</td>
<td>systemic-oral, IV (prednisone)</td>
</tr>
<tr>
<td></td>
<td>non-systemic-topical po/rectal (budesonide EC, budesonide foam)</td>
</tr>
<tr>
<td>Immunomodulators</td>
<td>Thiopurine (AZA, 6MP)</td>
</tr>
<tr>
<td></td>
<td>Mtx</td>
</tr>
<tr>
<td>Biologic</td>
<td>Anti-TNF(CZP, IFX, ADA)</td>
</tr>
<tr>
<td></td>
<td>Anti-integrin (VEDO)</td>
</tr>
<tr>
<td></td>
<td>Anti-IL12/23 inhibitor (Ustekinumab)</td>
</tr>
<tr>
<td>Small Molecules</td>
<td>Anti-SMAD7 antisense oligonucleotide (Mongerson)</td>
</tr>
<tr>
<td></td>
<td>topical</td>
</tr>
</tbody>
</table>
Different Release Sites and Release Mechanisms of 5-ASAs

Corticosteroids

- Need for steroids dictates subsequent outcomes
- Steroid dependence
- Induction therapy
- One of the most effective IBD medication
- Always try to minimize use
- Use non-systemic first
  - Budesonide MMX
  - Budesonide EC
- Taper from initiation of therapy
  - Flare
  - Until maintenance therapy effective
Corticosteroids

Potential side effects:

- Infection
- Hypertension
- Adrenal insufficiency
- Mood swings
- Osteoporosis

- Cataracts
- Weight gain
- Striae
- Diabetes mellitus
- Other

Vit D and bone density

Budesonide MMX in UC Induces Remission

Combined clinical and endoscopic remission at week 8.

### Optimizing Thiopurine Therapy

#### TPMT Measurement and Management

<table>
<thead>
<tr>
<th>TPMT Phenotype</th>
<th>Measurement</th>
<th>Levels</th>
<th>Management</th>
<th>Determine Thiopurine Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Do not use thiopurine</td>
<td>LOW</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>Decrease thiopurine dose by 1/3 to 1/2</td>
<td>INTERMEDIATE</td>
<td></td>
<td>80% response&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>High</td>
<td>Use</td>
<td>HIGH</td>
<td></td>
<td>Predict target dose + Likelihood of clinical response</td>
</tr>
<tr>
<td></td>
<td>2.5mg/kg body wt</td>
<td></td>
<td>If &lt;35, 81% response&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>If &gt;35, 43% response</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**WBC**

| Low            | Reduce or hold dose of thiopurine | LOW | If benefiting from thiopurine |
|                | Discontinue thiopurine | | If not benefiting |


### Optimizing Thiopurine Therapy

#### Thiopurine Metabolite Measurements and Management

<table>
<thead>
<tr>
<th>Thiopurine Nonresponder Groups</th>
<th>Metabolite Profile</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonadherent</td>
<td>Low/absent 6-TGN</td>
<td>Patient education</td>
</tr>
<tr>
<td></td>
<td>Low/absent 6-MMP</td>
<td></td>
</tr>
<tr>
<td>Underdosing</td>
<td>Low 6-TGN</td>
<td>Increase thiopurine dose</td>
</tr>
<tr>
<td></td>
<td>Low 6-MMP</td>
<td>Patient education</td>
</tr>
<tr>
<td>Thiopurine Resistant</td>
<td>Low 6-TGN</td>
<td>Switch to another drug. Possibly add allopurinol (special monitoring)*</td>
</tr>
<tr>
<td></td>
<td>High 6-MMP</td>
<td></td>
</tr>
<tr>
<td>Thiopurine Refractory</td>
<td>High 6-TGN</td>
<td>Switch to another drug</td>
</tr>
<tr>
<td></td>
<td>High 6-MMP</td>
<td></td>
</tr>
</tbody>
</table>

*WBC must be >4.5x10<sup>4</sup>*

Allopurinol dose is 100mg and thiopurine dose is reduced 25-50% from the original dose.

Efficacy of AZA as Maintenance Therapy in Adults With Refractory CD*

*Remission induced by prednisolone tapered over 12 wk


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Early AZA Alone Is Ineffective in CD

P = NS

Risk of Lymphoma with Thiopurine

- Significant after 1 year of exposure
- Highest absolute risk age >50
  - 1:354 cases /yr  RR=4.78
- Age <30 highest RR
  - SIR=6.99 (95% CI 2.99-16.4)
- Both sexes at increased risk; Men have a greater risk
  - SIR for men=4.50 (95% CI 3.71-5.40)
  - SIR for women=2.29 (95% CI 1.69-3.05)
- Men <30
  - SIR =~ 9


Steroid Sparing and Toxicity of MTX in Active CD

- Placebo (n = 47) vs. MTX 25 mg/wk IM (n = 94)
  - % Patients Able to Discontinue Steroids:
    - Placebo: 39%
    - MTX: 19%
  - % Patients Unable to Tolerate Medication:
    - Placebo: 17%
    - MTX: 2%
  - P = .025
  - P = .012

METEOR: Methotrexate vs Placebo in Steroid-dependent UC

**Week 16: Primary Endpoint**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=61)</th>
<th>MTX (n=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroid free remission</td>
<td>20%</td>
<td>32%</td>
</tr>
</tbody>
</table>

**Week 16: Secondary Endpoints**

**Baseline Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=61)</th>
<th>MTX (n=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone equiv. dose (mg/d)</td>
<td>30</td>
<td>25</td>
</tr>
<tr>
<td>Mayo score</td>
<td>4.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Mayo Endoscopy score</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

**METEOR: Conclusions**

- Parenteral MTX was not more effective than placebo for inducing steroid free remission at week 16 in patients with steroid dependent UC

- The rate of steroid free clinical remission at week 16 was higher with MTX than placebo

- MTX was well tolerated

- This trial did not investigate the efficacy of methotrexate as a maintenance therapy in UC. This is the purpose of an ongoing randomized trial, the MERIT-UC trial

Biologic Induction and Maintenance dosing

- Infliximab (IFX) 5 mg/kg IV @wk 0,2,6; then q 8 wks
- Adalimumab (ADA) 160 mg SQ wk 0, 80mg wk 2; then 40 mg SQ q 2 wks
- Certolizumab (CZP) 400 mg SQ wk 0,2,4; then 400 mg q4 wks
- Golimumab 200 mg SQ wk 0, 100 mg wk 2; then 100 mg q 4 wks
- Vedolizumab (VEDO) 300 mg IV wk 0,2,6 ;then q 8 wks
- Natalizumab 300 mg IV q 4 wks

- Ustekinumab single IV induction wt based dose; then 90 mg SQ q 8wks
  ≤55 kg -260 mg, ≥55 kg to 85 kg --390 mg; >85 kg - 520 mg

Biologic Treatment

- Induction dosing critical
- Avoid episodic dosing
- Dose optimization early
- Give in combination with immunomodulator (AZA,6-MP, MTX)
- Pre- treat IV dosing with hydrocortisone if not on immunomodulator
SONIC: Corticosteroid-Free Clinical Remission at Week 26
Infliximab

Patients with CRP $\geq$ 0.8 mg/dL and Lesions on Baseline Endoscopy (N = 204)

<table>
<thead>
<tr>
<th></th>
<th>AZA + placebo</th>
<th>IFX + placebo</th>
<th>IFX + AZA</th>
</tr>
</thead>
<tbody>
<tr>
<td>21/75</td>
<td>28.0</td>
<td>56.9</td>
<td>68.8</td>
</tr>
</tbody>
</table>


Infliximab in Ulcerative Colitis:
Clinical Remission*

*Clinical remission defined as Mayo score of $\leq$ 2 points, with no
Patients with baseline medication were continued on stable doses.


†P < 0.001
‡P < 0.01
CLASSIC: Clinical Remission and Clinical Response at 4 Weeks
Adalimumab

Remission is a CDAI ≤ 150   Response is a CDAI drop of ≥ 70

GAIN: Clinical Remission and Response at 4 weeks
with Adalimumab

Remission is a CDAI≤ 150   Response is a CDAI drop of ≥ 70
Adalimumab Induces and Maintains Clinical Remission in Patients With Moderate-to-Severe UC


Significant Improvement in Response and Remission at Week 26 with Certolizumab pegol: PRECISE 2

Combination Therapy with Infliximab and Azathioprine Works Better than Either Alone in UC


Accelerated Infliximab Dosing in UC

- Retrospective analysis
- 50 hospitalized severe acute UC patients
- 35 received standard IFX 0,2,6 – 42 days
- 15 received 3 doses: median - 24 days
- Standard induction:14/35=40% colectomy
- Accelerated induction:1/15=6.7% colectomy

Gibson, CGH 2015
Fecal Infliximab Loss

Week 2 clinical response (n=30)

P=.0047

CR w2 (n=18)
NR w2 (n=12)

Days after the first infliximab infusion


No Unanimity Regarding IFX Rescue Dosing for Severe UC

Induction dosing of IFX in severe ulcerative colitis

- 5 mg/kg body weight IFX week 0, 2, 6, then q 8 weeks: 24
- 10 mg/kg body weight IFX week 0, 2, 6, then q 8 weeks: 5
- 5 mg/kg with flexible timing of doses: 7
- 10 mg/kg with flexible timing of doses: 18
- Initial 10, then 5 mg/kg at week 2, 6: 7
- Initial 5, use 10 at week 2 if not doing well: 25
- Other: 14

Cyclosporine vs Infliximab

Cyclosporine was not superior to IFX in acute severe UC
(110 steroid refractory patients)

Golimumab in UC

Clinical Response at Week 6

Clinical Remission at Week 6

Placebo (n=251) Golimumab 200/100 mg (n=253)

Placebo (n=251) Golimumab 200/100 mg (n=253)

**Vedolizumab in UC**

**Week 6 and 52**

- Placebo (n=126)
- Vedolizumab 300 mg q8weeks (n=122)

Clinical remission at both Weeks 6 and 52

Primary Endpoint

<table>
<thead>
<tr>
<th>Placebo (%)</th>
<th>Vedolizumab (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>26%</td>
<td>47%</td>
</tr>
</tbody>
</table>

*P* <0.001

Secondary Endpoint

<table>
<thead>
<tr>
<th>Placebo (%)</th>
<th>Vedolizumab (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9%</td>
<td>21%</td>
</tr>
</tbody>
</table>

*P* =0.008

**Achieving Mucosal Healing With IFX Intensification**

- IFX Optimization and MH in UC and CD

<table>
<thead>
<tr>
<th>Increase in IFX level</th>
<th>% Mucosal Healing</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.6</td>
<td>0</td>
</tr>
<tr>
<td>0.6 - 1</td>
<td>6.5</td>
</tr>
<tr>
<td>1.5 - 3.4</td>
<td>30</td>
</tr>
<tr>
<td>&gt;3.4</td>
<td>60</td>
</tr>
</tbody>
</table>

*P* <0.001

Achieving Mucosal Healing With Monitoring and Medication Adjustment


Therapeutic Drug Monitoring Improves Durability of IFX Response

Prospectively optimized IFX trough concentration to target range of 5 – 10 μg/mL.

CYTOKINE CASCADE LEADS TO CHRONIC INFLAMMATION

IL-12 and IL-23 regulatory cytokines are overly expressed in Crohn's disease

This causes increased activation, proliferation and differentiation of immune cells T\(_{h}1\), T\(_{h}17\), and NK cells

...leading to increased production of proinflammatory cytokines, (Effector cytokines) such as TNF, IFN-\(\gamma\), IL-17, and others

UNITI 1 and 2: Clinical Remission through Week 8

In both studies all p values <0.05 except week 3 130mg dose

*Weight-range based UST doses: approximating 6 mg/kg: 250 mg (weight 100 kg), 200 mg (weight >55 mg and <125 kg), 150 mg (weight >125 kg).
**USTEKINUMAB – Week 52 Results**

**Clinical Response and Remission**

Anti-TNF Naive and Experienced

Patients randomized to placebo in the maintenance study received a single IV induction dose.

**Clinical Remission**

Anti TNF Naive vs Anti-TNF Experienced

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**Tofacitinib: Ulcerative Colitis (Phase III)**

- Tofacitinib 10mg bid (n=476) vs. placebo (n=122)*

**Week 8 Results**

* Octave I Study (similar data Octave 2)

Sanborn W et al. IDW 2016. #767
Ozanimod: Sphingosine 1-phosphate modulator in UC

Week 8 Outcomes

- 197 Patients
- Moderate to severe UC
- Randomized 1:1:1
- Dosage: mg/day
- Remission:
  - Mayo score ≤2; no subscore >1.
- Response:
  - Mayo score decreased ≥3 and > 30%; rectal bleeding score ≤1.


What About Safety?

- Mesalamine – rare issues, e.g. renal
- Immunomodulators- lymphoma, Infection
- Cyclosporine – infection
- Anti-TNF: Monotherapy vs. Dual-infection, malignancy, lymphoma (HSTL)
- Vedolizumab: Monotherapy vs. Dual-infection, lymphoma (dual)
What Is Our Treatment Target?

- Clinical - asymptomatic
- Biologic - normal labs, biomarkers
- Endoscopic - mucosal healing
- Histologic - deep remission

- Few of our patients are able to achieve it
  - Cost
  - Convenience
  - Efficacy
  - Side effects

Conclusion

- Existing strategies are frequently ineffective at long term disease control
- Prognostic factors are important to determine approach to therapy
- Careful disease and “Therapeutic Drug Monitoring” improve outcomes
- Need for optimization of current agents
- Need for new agents