Objectives

• Emphasize more recent changes in the approach to medical management of IBD
• Discuss basic principles of each class of therapy in IBD
• Provide optimization tips for each type of therapy
General Principles of IBD Management

• We are treating the result of the IBD, not the cause (as far as we know)- immune-based therapy
• Earlier is better
• Induction therapy usually dictates maintenance needs
• Severity of disease and burden of inflammation require more intensive therapy
• We are not curing IBD

Evolving Principles of IBD c.2016

• Incorporate elements of prognosis into diagnosis and medical decision making
• Moving beyond “one size fits all” to “smart therapy for the right patient”
• Precision medicine- optimization of treatments instead of “guesswork”
• Monitoring disease activity to achieve deeper remission and to anticipate flares
Drug Classes in IBD 2016

- **Aminosalicylates**
  - Oral
  - Rectal

- **Corticosteroids**
  - Systemic
  - Non-systemic
  - Rectal
  - Oral

- **Immunomodulators**
  - Thiopurines
  - Methotrexate

- **Antibiotics**

- **Biologics**
  - Anti-cytokines (Anti-TNF, Anti-IL12/23/6)
  - Anti-integrin (adhesion molecule inhibitors)

- **Investigational molecules**
  - Janus kinase inhibitors
  - Anti-SMAD7 antisense oligonucleotide
  - Sphingosine-1-phosphate receptor modulator

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Aminosalicylates

![Diagram of aminosalicylates and their metabolites](image)

- Sulfasalazine
- Sulfapyridine
- Mesalazine

- Bacteria in colon
- Metabolites

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General Principles of Aminosalicylates

• Effective for induction of mild to moderate UC (15-40%)
• Effective for maintenance of mild to moderate UC (58%-78%)
• Delivery-response relationship - get the drug to the location of the disease
• Very safe, but not completely safe (renal)\(^1,2\)
• Affected by payers now - substitution required that is not bioequivalent

Pearls for Optimization of Aminosalicylates

• Don’t forget 3% of patients intolerant/allergic\(^1\)
• Get the drug to the disease location
• Delivery systems may matter! If not responding, add or substitute a different delivery system\(^2\)
• Dose reduction when deep remission obtained is usually safe\(^3\)

\(^4\)Harris MS, Lichtenstein GR. *Aliment Pharmacol Ther.* 2011;33(9):996-1009.
**Dose Reduction after Induction is Safe if there is Mucosal Healing**

**MOMENTUM Trial**


- **Induction (8 weeks)**
  - MMX mesalazine 4.8g/day

- **Maintenance (12 months)**
  - MMX mesalazine 2.4g/day

*UC patients (n=717)*

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**Corticosteroids**

![Corticosteroids molecule](image)
Corticosteroids

- Revolutionary discovery in IBD\(^1\)
- Not sustainable
- Worst outcomes
- Prognostic- need for steroids dictates subsequent outcomes\(^2\)
- Understand steroid-dependence


Ulcerative Colitis

Mortality (%)

1938–1952
1953–1962
1963–1972
1973–1982
1983–1987

0 10 20 30 40

Corticosteroids introduced in 1952

Pearls for Optimization of Steroids

- Use non-systemic steroids first (also protects bones)\(^1\)
- Have an exit strategy
- Don’t lose the forest for the trees (“what’s the harm of one more course of steroids?”)
- Don’t forget vitamin D, bone density\(^1\)

Why Do We Taper Steroids?  
Is There Evidence For It?

- Prevention of adrenal crisis or adrenal insufficiency  
  - This is rare!  
  - 5 mg or less does not seem to cause adrenal insufficiency  
  - Higher doses are variable – 2 weeks of steroids unlikely to cause this

- Concern for disease relapse or “rebound” - *no evidence*

- Practical approach: taper over duration of induction period OR duration of time for maintenance therapy to work


Immunomodulators
Thiopurines

- Genetically determined metabolism
- Steroid sparing
- Lymphoma risk well known (Schwartz)
  - HR 5.28 (95% CI, 2.0-13.9)\(^1\)
  - Back to baseline after stopping\(^2\)
  - Consider EBV testing for patients <20 yo

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Early AZA Therapy is Not More Effective Than Placebo or Conventional Therapy for CD

Actuarial probability of survival free relapse. Defined as CDAI >175 in patients treated with azathioprine and placebo.


Proportion of patients in corticosteroid-free remission per trimester over time. Concomitant proportions were significantly different only at trimester 3 (P<.05).

Pearls for Optimization of Thiopurines

- No prospective data on optimization
- Intermediate metabolizers do better!
- Metabolites can be helpful\(^1\) (Siegel)
  - Remember allopurinol\(^2\)
- Bedtime or split dosing if nausea predominant
- Pancreatitis is genetically determined too\(^3\)


Methotrexate

- Our colleagues are not as comfortable using it
- Effective for induction and maintenance of Crohn’s disease\(^1\)
- Limited by toxicity/side effects\(^2\)
- Relatively contraindicated in menstruating females
- No data for its use as salvage therapy after failing anti-TNF therapy

Pearls for Methotrexate

- Equal bioavailability PO up to 15 mg
  - ≥12.5 mg/w gives preferred outcomes in combination with anti-TNF
- Use ondansetron as a pre-med (30 minutes before MTX)
- Take it on weekends
- Don’t forget folic acid! (1-2 mg/day)
- Monitor liver enzymes every 6 months (but safe)

Anti-TNF Therapies for IBD

- Certolizumab pegol (CD)
- Adalimumab (CD, UC)
- Golimumab (UC)
- Infliximab (CD, UC)


Anti-TNF Biological Therapies

- Revolutionary in IBD
- Loading and maintenance needed
- Known risks of non-response or loss of response
- Important role for therapeutic drug monitoring (Siegel)
Pearls for Optimization of Anti-TNFs

• Routine assessment of stability between doses
• Understanding difference between class effect non-response and individual drug effect (swapping vs. cycling)
• Combination therapy mostly accepted as superior\(^1,2\)


Higher Response and Remission Rates with Anti-TNFs in Patients with Shorter Disease Duration

• Infliximab for CD:
  – Pediatric response/remission = 90%/60\(^1\)
  – Adult response/remission = 66%/39\(^2\)
• Adalimumab/certolizumab pegol for CD\(^3,4\):
  – Post-hoc
  – Shorter dz duration = better response
• Adalimumab maintenance\(^3\)
  – Less with shorter dz duration
• Claims data\(^5\)
  – Shorter time to anti-TNF = less time to surgery, steroids

Biosimilars

- Inflectra, biosimilar to infliximab (Remicade), approved by the FDA on April 5th, 2016\(^1\)
- Amjevita, biosimilar to adalimumab (Humira) approved by the FDA on September 28th, 2016\(^2\)
- Infliximab biosimilar available in EU since 2013\(^3\)


- Several ongoing studies in Europe and Asia
- Evidence that unidirectional switches are safe\(^1-7\)
- Still not available in the USA

"Biosimilars are Here! What Every Gastroenterologist Needs to Know"
- Tuesday, October 18th 11:30-11:50AM
- Annual Scientific Meeting – 3B
Anti-integrins

Natalizumab Vedolizumab

300mg IV q4W

300mg IV at weeks 0, 2, and 6 then 300 mg IV q8W

CD CD UC

Pearls for Anti-integrins

• You still need to check for TB and HBV prior to insurance approval! (not because of risk but because insurance companies are ignorant and require it)

• There are some patients who develop joint pain after starting therapy, unclear if this is:
  – Side effect of medication
  – “uncovering” parallel joint problems in IBD patients that were otherwise treated with systemic therapy
  – Withdrawal from steroids

• We have not had much difficulty getting dose escalation to monthly infusions
  – I have usually tried monthly infusions for 3-4 months before making a decision to stop trying this mechanism

No Additional Benefit to Combination Therapy in Pivotal Trial of Vedolizumab

Clinical remission in Crohn’s Disease patients at week 6 by week 0 concomitant medication use: ITT Population

Where Should We Position Anti-Integrin Therapies?

- In patients unresponsive or intolerant to conventional therapies and anti-TNF agents
- In patients with unusual or other immune conditions such that additional systemic immune modification may be relatively contraindicated
  - Organ transplant patients
  - Hereditary or acquired immune deficiencies
- Other possibilities:
  - The older patient
  - Before systemic therapies?
  - Combination with calcineurin inhibitors
Anti-IL 12/23 (Ustekinumab)

- Approved by the FDA for moderate to severe Crohn’s disease on Sept 26, 2016

- Dose
  - Initial weight-based IV dose:
    - ≤55 kg: 260 mg IV
    - >55 kg to 85 kg: 390 mg IV
    - >85 kg: 520 mg IV
  - Maintenance dose:
    - 8 weeks after initial, 90mg SC q8w

Ustekinumab (anti-IL12/23) for Moderate to Severe CD

- Effective for induction with clinical response rates at week 6 compared to placebo (23.5%)\(^1\)
  - 36.6% (1mg/kg)
  - 34.1% (3mg/kg)
  - 39.7% (6mg/kg)

Safety of Ustekinumab Through 44 Weeks
IM-UNITI

- No notable new safety issues identified
- No deaths or serious opportunistic infections
- 2.3% of patients developed antibodies, but these did not preclude drug efficacy

<table>
<thead>
<tr>
<th>Subjects With (%)</th>
<th>Placebo</th>
<th>90 mg SC Q12w</th>
<th>90 mg SC Q8w</th>
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</thead>
<tbody>
<tr>
<td>Death</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>AEs</td>
<td>83.5%</td>
<td>80.3%</td>
<td>81.7%</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>15.0%</td>
<td>12.1%</td>
<td>9.9%</td>
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<tr>
<td>Serious Infections</td>
<td>2.3%</td>
<td>5.3%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Discontinuation due to AE</td>
<td>6.0%</td>
<td>7.6%</td>
<td>3.1%</td>
</tr>
<tr>
<td>Malignancies</td>
<td>0.8%</td>
<td>0%</td>
<td>0.8%</td>
</tr>
</tbody>
</table>

AE, adverse event; Q8w, every 8 weeks; Q12w, every 12 weeks

Summary: IBD Drug Therapy 2016

- Goals of management are evolving: use prognosis, target deep remission.
- For 5-ASAs understand delivery and possible dose-reduction in maintenance.
- You don’t need to taper steroids as much as you think.
- Lymphoma is from thiopurines, goes away when these drugs are stopped.
- Pro-active anti-TNF drug monitoring is coming soon.
- Biosimilars are coming soon... Interchangeability is uncertain.
- Anti-integrin therapies are safe and probably should be used earlier, at least in UC.
- Anti-IL12/23 is shown to be effective in induction and maintenance of moderate-to-severe CD as maintenance therapy.