Changing Medications versus Surgery: Decision Making in Inflammatory Bowel Disease

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ARS Question #1

Which of the IBD treatments has the highest reported side effects and safety/toxicity concerns?

A) Mesalamine/5ASA (i.e. Asacol, Lialda, Pentasa, etc)
B) Steroids (corticosteroids, prednisone)
C) Thiopurine (Azathioprine, Imuran, 6 mercaptopurine)
D) Anti-TNF Biologics (i.e. Remicade, Humira, Cimzia, Simponi)
ARS Question #2

- Which statement regarding IBD and Surgery is TRUE?
- A) Everyone with IBD will have surgery at least once in their lifetime
- B) Crohn’s disease is cured after surgery
- C) Surgery should be considered in all patients who do not want to be on steroids/prednisone for a long time
- D) Surgery may help treat complications of Crohn’s disease or ulcerative colitis
Learning Objectives

- Review Inflammatory Bowel Disease (IBD) 101
- Discuss treatment options in IBD
- Understand efforts to optimize medications
- Review role of surgery in IBD
What is the Immune System?

- Cells (T cells, B cells, macrophages) that defend the body against attack from infections
- To eradicate infection, the immune system causes inflammation
- Once an infection is eliminated, the immune system knows how to turn itself off

Photo courtesy of Scott Plevy, MD
Dysregulated Immune System

- In IBD, the “off” switch is broken
- Inflammation is a Key Aspect of IBD
Chronic Inflammation:
Proteins Called Cytokines Are the Light Switch

“On”

“Off”
IBD 101: TWO MAIN TYPES

**Ulcerative Colitis**
- Contiguous & circumferential
- Superficial inflammation
- Erythema, Edema
- Loss of vascular pattern
- Friability
- Granularity

**Crohn’s Disease**
- Discontinuous, patchy, full-thickness inflammation
- Mouth-to-anus involvement
- Strictures
- Fistulas and abscesses
ILEOCOLONOSCOPY

Normal findings of terminal ileum and colon
UC - Spectrum of Disease

Normal

Mild

Moderate

Severe
CD: Spectrum of Disease
Spectrum of IBD

Crohn’s Disease

Indeterminate Colitis

Ulcerative Colitis
Spectrum of IBD

Crohn’s Disease

Ulcerative Colitis

Indeterminate Colitis
The “-omes” in IBD Pathogenesis

Taken from Fiocchi C. Dig Dis 2015
Right Patient, Right Treatment, Right Time

- Integration of clinical variables (i.e. age, gender), disease characteristics, genetic and conventional laboratory testing to guide treatment decisions - INDIVIDUALIZE

- Decrease risk of adverse events and disease complications
- Potential to optimize efficacy and outcomes
- Similar model used: Diabetes, hypertension
Why do we need Personalized Medicine in IBD?
Learning Objectives

- Review Inflammatory Bowel Disease (IBD) 101
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Early, Consistent IBD Treatment = Increased Chance of Staying Well

- Health
- Subclinical Inflammation
- Symptomatic Inflammation
- Complications
- Disability

Disease Prevention
Prevention of symptomatic disease
Prevention of complications
Prevention of relapse

About IBD. CCFA
IBD Medicine Cabinet

- Over-the-Counter
- Antibiotics
- Aminosalicylates/Mesalamine
- Corticosteroids, Budesonide
- Immunomodulators – AZA/6MP, MTX
- Biologics: Anti-TNFs/Anti-Adhesions/Anti-Interleukins
**Top-down** Strategy
- Early, appropriate use of biologic as initial treatment
- Induces rapid clinical response
- May enhance quality of life

**Bottom-up** Strategy
- Standard, sequential treatment for remission and maintenance
- Cost-effective
- Minimal side effects
Treatment Approach Strategies

Low risk of disease progression

High risk of disease progression

‘Top-down’: may over-treat and expose patients to costs, risks of immunosuppression

‘Step-up’: may postpone adequate therapy in aggressive disease and results in disease progression, complications, morbidity
Update in the Evolution of Treatment Goals & Strategies

- Improved clinical symptoms
- Clinical remission
- Steroid free remission
- Mucosal healing
- Histologic remission

Adapted CCFA Canada Webinar 2015
THE EVOLUTION OF CROHN’S DISEASE: INFLAMMATION LEADS TO DAMAGE

Over a 20-year period, 88% risk of developing stricturing (18%) or penetrating (70%) disease

Cosnes J et al. Inflamm Bowel Dis. 2002
Variables at Diagnosis Associated with Aggressive CD

- Younger age (<40 years)
- Perianal disease
- Stenotic disease

Most Important Predictors:
- Disease Location
- Disease Extent
- Depth of inflammation or lesion

- Deep ulcerations
- Higher titers of ASCA, anti-OmpC, and anti-CBir1
- Mutations in the NOD2/CARD15, ATG16L1, and MDR1 genes
Natural History: Most Crohn’s Patients Will Require Surgery

## Variables at Diagnosis Associated with Aggressive CD

- Disease Location
- Disease Extent
- Depth of inflammation or lesion

## Variables at Diagnosis Associated with Aggressive UC

- Younger age (<40 years)

### Most Important Predictors:
- Disease Extent
- Age at onset
- Incomplete response to steroids and 5-ASAs/mesalamine
- Higher levels of pANCA

Falvey JD, et al. IBD 2015
Natural History Of Ulcerative Colitis

Risk of colectomy:  24% after 10 years  
~ 30% after 20 years

Significant Increased risk of cancer

Adapted from Langholz E, et al. *Gastroenterol* 1994
New Therapies have and will be designed to Target specific –
• Inflammatory proteins (TNF best example)
• Genetic defects
• Microbial imbalances

Directly target what is responsible for the disease process – the inflammatory cascade
### New Targets: Mechanisms of Action Biologics IBD

<table>
<thead>
<tr>
<th>Biologics</th>
<th>Indication</th>
<th>Approval Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>CD</td>
<td>1998</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>CD</td>
<td>2002</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>UC</td>
<td>2012</td>
</tr>
<tr>
<td>Certolizumab pegol</td>
<td>CD</td>
<td>2008</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>CD</td>
<td>2008</td>
</tr>
<tr>
<td>Vedolizumab</td>
<td>UC &amp; CD</td>
<td>2014</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>CD</td>
<td>2016</td>
</tr>
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<td>Golimumab</td>
<td>UC</td>
<td>2013</td>
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</table>
Protein Target Specific: Biologics in IBD

• Revolutionized treatment and management of UC and CD

• Why do we use them?
  – Very effective
  – Reduces hospitalization, surgery
  – Steroid free remission
  – Improved quality of life
  – Changes the natural history of disease**

• Limitations: costs, misinformation
Since introduction of biologic agents/anti-TNFs, decrease in total colectomy in UC patients

Kaplan GG et al. AJG 2012
Safety/Toxicity of Anti-TNFs

- Stopped therapy due to adverse event: 10%
- Infusion or injection site reactions: 3% to 20%
- Drug-related lupus-like reaction: 1% (1/100)
- Serious infections: 3% (3/100)
- Tuberculosis: 0.05% (5/10,000)
- Non-Hodgkin’s lymphoma (combo): 0.06% (6/10,000)
- Multiple sclerosis, heart failure, serious liver injury: Case reports only

Siegel CA, et al. Inflamm Bowel Dis. 2010
Risks of Anti-TNFs and Immunomodulators

If 10,000 patients were treated for 1 year

<table>
<thead>
<tr>
<th>Event</th>
<th>Estimated Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHL (baseline)</td>
<td>2/10,000</td>
</tr>
<tr>
<td>NHL (on IMs)</td>
<td>4-9/10,000</td>
</tr>
<tr>
<td>NHL (on anti-TNF with prior IMs)</td>
<td>4-9/10,000</td>
</tr>
<tr>
<td>Hepatosplenic T-cell lymphoma</td>
<td>Unknown</td>
</tr>
<tr>
<td>Death from sepsis (lower for younger patients)</td>
<td>4/1,000</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>5/10,000</td>
</tr>
</tbody>
</table>

Anti-TNF, anti-tumor necrosis factor; IMs, immunomodulators; NHL, non-Hodgkin lymphoma.
Table adapted from Siegel CA. In Inflammatory Bowel Disease: Translating Basic Science Into Clinical Practice. Wiley, 2010.
Risk for Cancer - Lymphoma
Safety/Toxicity of Anti-TNFs

- Serious Infections in Crohn’s disease
  - Anti-TNF increases risk 43%
  - Prednisone increases risk 57%
  - Opioid use doubles the risk
  - Active Crohn’s Disease - Moderate to severe more than doubles the risk
Learning Objectives

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A New Era in IBD: Therapeutic Drug Monitoring (TDM)

- ~50% IBD patients will require dose modification or switch of treatment (~1yr)
- ~30% are primary nonresponders to antiTNFs
- Symptoms may not be correlated with active inflammation (endoscopy vs CRP)
- Need to identify patients with
  - Insufficient drug
  - Anti-drug antibodies
  - Causes other than active IBD
Therapeutic Drug Monitoring: Guide to optimize medical treatment

High detectable antibodies

Change to another anti-TNF

Sub-therapeutic anti-TNF drug level

Increase dose or frequency of anti-TNF

Therapeutic drug level, low/no antibodies

Scope, lab, imaging – active or inactive disease?
Active -> switch class of biologic therapy

Afif W et al. Am J Gastro 2010
Subjective vs Objective: Clinical versus Endoscopic Indices

- Does not correlate with clinical course of disease
- Does not prevent long-term complications of disease

Impact of Mucosal Healing (MH): Surgical Outcomes

- Crohn’s Disease (CD)
- Ulcerative Colitis (UC)

Timing for IBD

Cumulative Probability (%)

Penetrating

Inflammatory

Stricturing

Cosnes J et al. Inflamm Bowel Dis. 2002
Learning Objectives

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Indications for Surgery

- **Intractability** (most common indication)
  - Debilitating symptoms – obstruction, stricture, fistula, pain
  - Poor or no response to medical therapies

- **Dysplasia** – (pre)cancer

- **Massive colonic bleeding**
  - Uncommon event, representing <5% of patients requiring operation
  - Subtotal colectomy usually suffices, proctectomy only if bleeding refractory

- **Toxic megacolon**
  - IVF, NGT, stress-dose steroids, broad-spectrum antibiotics
  - Deterioration or lack of improvement w/in 72 hrs -> surgery
  - Total abdominal colectomy w/ ileostomy, Hartmann’s pouch
Goals of Surgery

- Surgery and medication can combine for better quality of life
- Primary goals of surgery
  - Alleviate complications
  - Alleviate symptoms
  - Achieve best possible quality of life
  - Bowel conservation
Surgery Indications in IBD
Inflammation -> Fistula, Stricture

Taken from M. Shaikhani MD
Elective Surgery

- Crohn’s Disease
  - Formation of fistula, abscess
  - Stricture
  - Dysplasia - (pre) cancer
  - Excessive bleeding in intestine
  - Failure of medications to control disease

- Ulcerative Colitis
  - Dysplasia
  - Failure of medications to control disease
Timing of Surgery: Meatloaf vs Chicken

- When there is active inflammation, the risks for surgery complications increases:
  - Leakage of bowel content; infection; wound dehiscence
Emergent Surgery

- **Crohn’s Disease**
  - Perforation of the bowel
  - Intestinal obstruction or blockage

- **Ulcerative Colitis**
  - Perforation of colon
  - Toxic megacolon
  - Excessive bleeding
## Types of Surgery in IBD

<table>
<thead>
<tr>
<th>Crohn’s Disease</th>
<th>Ulcerative Colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Strictureplasty</td>
<td>• Proctocolectomy (removal of the colon and rectum)</td>
</tr>
<tr>
<td>• Resection of small intestinal segment</td>
<td>– With ileostomy</td>
</tr>
<tr>
<td>• Colectomy (partial or complete)</td>
<td>– Restorative (ileoanal or J pouch)</td>
</tr>
<tr>
<td>• Proctocolectomy</td>
<td>– Disease is “cured” once the colon is removed</td>
</tr>
<tr>
<td>• Diverting colostomy or ileostomy</td>
<td></td>
</tr>
<tr>
<td>• Unlike UC, CD cannot be cured with surgery</td>
<td></td>
</tr>
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</table>
Ulcerative Colitis: IPAA, J Pouch

Taken from ucstory.wordpress.com
## Risks of Surgery

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<thead>
<tr>
<th>Crohn’s Disease</th>
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<tr>
<td>• Complications, as with any surgery</td>
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</tr>
<tr>
<td>• Psychological implications for those with a stoma</td>
<td>• Potential complications specific to IPAA include:</td>
</tr>
<tr>
<td>• Recurrence of disease:</td>
<td>– Pouchitis</td>
</tr>
<tr>
<td>• - Endoscopic: 70-90%</td>
<td>– Small bowel obstruction</td>
</tr>
<tr>
<td>• - Symptoms: 30% 3yr, 60% 5 yr</td>
<td>– Pouch failure (8%-10% of patients)</td>
</tr>
<tr>
<td>• - Tissue: 50% by 5 yr</td>
<td>– Difficulty getting pregnant, infertility</td>
</tr>
<tr>
<td></td>
<td>• Psychological implications for those with ileostomy</td>
</tr>
</tbody>
</table>
Personalized Medicine Algorithm

Treatment
Optimize ongoing drug switch intra/other class Add drugs

Active disease (including mucosal ulceration) Risk stratification

2-3 months*

6 months*

Target
- No symptoms
- No positive surrogate marker (CRP, +/- fecal marker)
- No mucosal ulceration

NO

YES

1-2 year(s)

Continue treatment

Questions