Medical Management of Inflammatory Bowel Disease

Freddy Caldera D.O.
Assistant Professor
Division of Gastroenterology

Objectives
- Discuss Crohn’s disease and Ulcerative Colitis
- Discuss Medications for Inflammatory Bowel Disease
- Treatment goals for Inflammatory Bowel Disease
- Review appropriate Vaccination for IBD population.

Inflammatory Bowel Disease
- Conditions characterized by chronic or relapsing immune activation and inflammation within the gastrointestinal tract.
- Crohn’s disease and ulcerative colitis (UC) are the two major forms of idiopathic IBD
- Less common, but increasingly recognized, are the microscopic colitis primarily: collagenous colitis and lymphocytic colitis

Inflammatory Bowel Disease
- Is NOT
  - An Allergy
  - An immune deficiency
- Is
  - Inflammatory active immune system in the intestinal tract
  - Chronic – last a long time (maybe lifetime)
  - Treatable

Current Etiologic Hypothesis for IBD

Inflammatory Bowel Disease (IBD)
- Approximately 1.4 million Americans have IBD
- 70,000 new cases each year

Selby Inflamm Bowel Dis. 2008:14:253-58
Incidence of IBD < 1960

Incidence 1980-2008

Epidemiology of IBD

Onset of IBD

What is Ulcerative Colitis?

Ulcerative colitis location and extent

- Inflammatory bowel disease involving the large intestine (colon and rectum)
- Variable extent of large bowel involvement
- Almost always starts in the rectum and may involve more bowel or progress proximally
- Major symptoms usually come from the inflamed rectum
- Disease is characterized in most patients by active inflammation alternating with periods of quiescence (remission)
- Cause remains unknown, triggers of onset are usually not identifiable.

**Presentation of UC**
- Symptoms depending on extent and severity of inflammation
- Bloody diarrhea
- Abdominal cramping
- Tenesmus – fecal urgency
- Systemic symptoms, fever, decreased stamina, weight loss

**Natural history of UC**
- Disease progress in 54% of patients within 5 years of diagnosis
- Complications highest among pancolitis patients
- 20-38% ultimate require proctocolectomy
- Increased risk of colon cancer

**Ulcerative Colitis Disease Activity**

**What is Crohn’s disease?**
- Inflammatory bowel disease involved the entire GI tract (mouth to anus)
- Disease is characterized in most patients by patchy inflammation which alternates between periods of active disease and periods of quiescence.
- Inflammation is full-thickness
- Fistulas and strictures occur
- Symptoms depend on extent and severity of disease

**Clinical presentation of Crohn’s disease**
- Ileocecal disease: abdominal pain, diarrhea, fever
- Colonic disease: bloody diarrhea, weight loss, fever
- Perianal disease: pain, fistulae, fissures

**Crohn’s disease location and extent**
- Mouth to Stomach: 6%
- Colon: 32%
- Ileocolitis: 45%
- Rect: 22%
### Clinical Criteria for Crohn’s Disease Activity

- **Mild to moderate disease**
  - Ambulatory, no abdominal tenderness, painful mass, or obstruction
- **Moderate to severe disease**
  - Unresponsive to treatment for mild to moderate disease with prominent fever, weight loss, anemia, abdominal pain and tenderness or intermittent nausea or vomiting
- **Severe fulminant disease**
  - Persistent symptoms on corticosteroids or with high fever, rebound tenderness, cachexia or abscess

### What is clinical remission?

- A) Getting rid of all inflammation
- B) Achieving symptom relief
- C) Curing the disease
- D) Decrease symptoms

### What drug classes are available for treatment?

- Aminosalicylates
- Immunomodulators
- Biologics
- Non-TNF Biologics
- Steroids

### Induction Therapy

- Induction
  - Achieve quick treatment response and clinical remission
  - Decided based on severity of disease
- Options
  - Aminosalicylates
  - Steroids
  - Anti-TNF Agents (Biologics)

### Maintenance Therapy

- Maintenance
  - Prevents relapses and maintains long term clinical remission
  - Therapy depends on severity of disease
  - Corticosteroid sparing therapy
- Options
  - Aminosalicylates
  - Immunomodulators
  - Anti-TNF Agents (Biologics)
  - Non-TNF Biologics

### Goals of Therapy

- Establish and maintain symptom control (clinical remission)
- Control inflammation
- Prevent flare-ups of disease (maintain remission)
- Reduce complications
- Reducing the need for surgery
- Improve quality of life
- In children facilitating normal growth
Crohn’s Disease: 1960’s historical perspective

Principles of IBD Treatment
- Since it’s an autoimmune condition most cases are treated with immunosuppressant.
- Mild cases can be treated with non-immunosuppressant’s.
- Steroids are temporary and do not make inflammation better.

Aminosalycilates
- Sulfasalazine initially developed to treat rheumatoid arthritis by Swedish physician Nana Svartz in 1938
- Effective in inducing and maintain clinical remission:
  - Mild to moderate Ulcerative Colitis
  - Mild Crohn’s disease affecting Colon

Serious Potential Adverse Effects From Prolonged Corticosteroid Therapy
- Infection
- Hypertension
- Diabetes
- Osteonecrosis
- Osteoporosis
- Myopathy
- Cataracts
- Gastric Ulcer
- Glaucoma
- Psychosis

Use of corticosteroids in IBD should always have an effective exit strategy.

Immunomodulators
- Two commonly used are Methotrexate and Azathioprine
- Steroid sparing agents
- 6MP/Azathioprine
  - Developed in the late 50 and early 60 by George Hitchings and Gertrude Ellis
  - Used in Childhood leukemia and Organ transplantation
  - Used since the 1980
- Methotrexate
  - Used in rheumatoid arthritis
  - Evidence that its effective in Crohn’s disease
6MP/Azathioprine Efficacy

- Effective in moderate Crohn’s and Ulcerative Colitis
- Can take 3-4 months to work
  - Maintenance Therapy
  - Remission rates 30-40%

Methotrexate Efficacy

- Effective in maintain clinical remission in moderate Crohn’s disease
- Delivered SQ or IM
- Folate supplementation is needed
- Not PO (like used by rheumatologist)
- Maintenance Medication
  - Effective 30-40% of the time

**TNF inhibitors Mechanism of Action**

- Interfere with body inflammatory response targeting specific cytokines
- Targeted treatment as opposed to corticosteroids provide more general suppression
- Work by binding and preventing activity of tumor necrosis factor alpha (TNF-alpha)
- TNF cytokine promotes inflammation in intestine and other organs.

**TNF inhibitor Efficacy**

- Effective in inducing and maintaining clinical remission in severe Ulcerative Colitis and Crohn’s disease.
- SQ or IV
- One year maintenance rates of 40-50%

**Anti-integrin**

- Mainly acts by affecting white blood cell migration
- Natalizumab efficacious for Crohn’s disease and Multiple sclerosis
  - Rare side effect of PML limits it use
- Vedolizumab
  - Gut specific
  - No Risk of PML
  - FDA approved for Crohn’s and Ulcerative Colitis
Selective anti-adhesion molecules: Rationale

Conventional and evolving treatment strategies in CD

Early top-down biologic therapy vs conventional management of Crohn's disease

Remission With No Corticosteroid Therapy

Weighing the Value of Top-Down Therapy

Benefits

- Early promotion of mucosal healing to prevent complications
  - Evidence of 6-MP/AZA and infliximab promoting mucosal healing
- Serious side effects
- Development of antibodies (biologics)
- Cost
- Majority of patients do not require more potent treatments initially

Advantages

- Conventional
- Early Aggressive

Conventional and evolving treatment strategies in CD

Remission With No Corticosteroid Therapy

Top-Down vs Step-Up


The impact of CE studies: SONIC:

Corticosteroid-Free Clinical Remission at Week 50

Patients who did not enter the study extension were treated as nonresponders.
Early "top-down" therapy with azathioprine is not more effective than placebo or conventional therapy

Mucosal Healing and Time to Colectomy in Infliximab-treated Patients: Endoscopy Subscore

The Natural Course of Postop CD

>70% of Patients have i2,3,4 Recurrence 1 Year

Preventive care Recommended?
- 26yo with newly diagnosed Crohn’s disease with ileal and perianal disease starting TNF therapy
- What preventive measures would you recommend?
Why do it matter?
- Many patients with IBD are young and do not have co-morbid illnesses
- Patients with IBD receive less preventive health services than the general primary care patients

Risk of Infection in IBD
- Infections are the most common significant adverse event among immunosuppressed patient with IBD
- Risk of serious infection increases with the number of immunosuppressive therapies
- Steroids
- Many infections are preventable with routine preventive immunizations.

Serious Infection Risk with TNF-α vs. non-biologics

<table>
<thead>
<tr>
<th>Table 2. Infliximab vs. Adalimumab and Risk of Serious Infections*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exp</strong></td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td><strong>TNF-α antagonists</strong></td>
</tr>
<tr>
<td><strong>F·X·Z vs. non-biologics</strong></td>
</tr>
<tr>
<td><strong>Relative risk (CRS)</strong></td>
</tr>
</tbody>
</table>

Vaccination
- Goal: prevent infections in a population that is often immunocompromised
- Influenza and pneumococcal pneumonia are the most common vaccine preventable illnesses in adults
- Standard recommended immunization schedule for adults should be adhered to
- At diagnosis, all adults should have review of immunization history, with catch up vaccination given as needed
- Exceptions
  - Live virus vaccines
    - Contraindicated with immunosuppression

Immunization of IBD Patients
- All patients should get influenza vaccination
- All patient should get vaccinated with pneumococcal vaccine
- Patient on Immunossuppression should receive new 13 serotype followed by 23 serotype vaccine
- Young males and females vaccinated for HPV.

Patients with IBD are under-vaccinated
- 169 patients surveyed at Tertiary IBD Center
- 98% reported current or past immunosuppressant use
- 28% received regular influenza shots
- 9% had pneumococcal vaccination
- 45% tetanus vaccine in past 10 years
- Most common reason for non-immunization
  - Lack of awareness (49%)
Increased risk of Pneumonia in IBD

Retrospective national cohort

108, 604 IBD vs. 434,416 non IBD

Smoking Cessation in IBD Patients

- Crohn’s and UC patient should be counseled to quit.
- Increased prevalence of Crohn’s disease in smokers
- Crohn’s disease patients who are smokers
- More severe ileal disease, more frequent flares, an increased need for steroids and immunomodulator and higher rates of surgery

Cutting back or Quitting Helps

- Smoking cessation is crucial aspect in the management of Crohn’s patients that if often overlooked
- Decreased risk of relapse
- Decreases need for steroids or immunomodulator

Summary: Take Home Points

- Steroids are temporary medication for IBD
- Medical treatment of IBD goals to achieve prolonged clinical remission.
- We are never going to prevent all infections
- But, we have an opportunity to prevent serious infectious complications by thoughtful patient selection and vaccination
- Advise smokers to quite smoking

THANK YOU

- Questions?
  - fcaldera@medicine.wisc.edu

- New Multi-Disciplinary IBD clinic
  - complicated patients seen by
    - IBD specialist
    - Colorectal Surgeon.
    - Ostomy nurse