Pharmacotherapy of Crohn’s and Ulcerative Colitis

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Pharmacist Objectives

- Classify patients based on the severity of the disease
- Identify pharmacokinetic/pharmacodynamic properties of current drug therapies
- Formulate an appropriate pharmacotherapy regimen based on patient’s severity classification

Technician Objectives

- Distinguish between Ulcerative Colitis (UC) and Crohn’s Disease (CD)
- List the signs and symptoms patients with UC and CD may experience
- Identify the current drug therapies available for UC and CD treatment

Disclosure

The author of this presentation has no current affiliation with any organization, manufacturer, or financial incentives. There is nothing to disclose.
Ulcerative Colitis (UC)

Introduction

- UC is a chronic disease characterized by mucosal inflammation limited to the colon
  - Rectum involvement occurs in 95% of cases
- Approximately 500,000 individuals in US suffer from UC
  - About 8-12/100,000 people per year with be diagnosed with the disease
- Direct medical cost exceed $4 billion dollars annually
  - Hospitalizations account for about $960 million dollars

The Guidelines

- Ulcerative Colitis Practice Guidelines in Adults: American College of Gastroenterology (2010)
- Management of Crohn’s Disease in Adults American College of Gastroenterology (2009)

Signs/Symptoms

- Hallmark presentation:
  - Bloody diarrhea
    - +/- rectal urgency and tenesmus
- Differential diagnosis:
  - UC (new or exacerbation)
  - Infective colitis
  - Clostridium difficile (C. diff)
Diagnostic Tools

- Stool examinations
  - Used to rule out c.diff

- Sigmoidoscopy/colonoscopy
  - Reveals the mucosal changes associated with UC
    - Loss of typical vascular patterns, granularity, friability, and ulcerations

- Biopsy
  - Is necessary if colonoscopy results are not specific for UC
  - UC mucosa will show separation, distortion, and atrophy of crypts

Classification of Severity

- Mild disease:
  - < 4 stools/daily (+/- blood)
  - No systemic signs of toxicity
  - Normal erythrocyte sedimentation rate (ESR)

- Moderate disease:
  - > 4 stools/daily
  - Minimal signs of toxicity

- Severe disease:
  - > 6 bloody stools/ daily
  - Evidence of systemic toxicity

- Fulminant disease
  - > 10 stools/daily
  - Continuous bleeding (blood transfusion requirements)
  - Abdominal tenderness and distention

Goals of Treatment

- GOAL: Promote healing, reach disease remission, improve quality of life
  - Endoscopic demonstration of mucosal healing is not ALWAYS necessary

- Type of treatment depends on:
  - Anatomic extent of the disease
    - Limited to below the descending colon (distal)
    - Extends to the descending colon (proximal)
  - Severity of the disease
    - Mild, moderate, severe, or fulminant
  - Global assessment of the patient
    - Quality of life
      - School, work, relationships, anxiety
    - Extraintestinal manifestations (EIM)
      - Ocular complications, peripheral arthropathies, dermatological changes

Normal vs. Ulcerated

- Normal mucosa
- Ulcerated mucosa
Aminosalicylates Class

• Active ingredient is 5-aminosalicylic acid
• MOA:
  – Inhibition of cytokine synthesis by inducing PPAR-gamma gene expression which suppresses the activation of cytokine NFkβ and toll-like receptors (TLRs)
  – Inhibition of prostaglandin and leukotriene synthesis by inhibiting cyclooxygenase (COX) and lipoxygenase enzymes
  – Free radical scavenger
  – Immunosuppressive activity the block lymphocyte DNA synthesis and cell cycle progression

Aminosalicylates Class

• Agents:
  – Azulfidine® (sulfasalazine)
    • 4-6 g/day divided into 4 doses
    • Prodrug needs to be converted to 5-ASA
    • Onset of action ~ 3 to 4 weeks
    • Absorption ~ 10-15% in small intestine
    • Intolerance is very common due to sulfapyridine moiety
    – N/V, dyspepsia, and headache
    • Adverse effects
      – Allostatic reactions, pancreatitis, hepatotoxicity, interstitial nephritis, hemolytic and megaloblastic anemia
  – Colazal® (balsalazide)
    • 6.75 g/day divided into 3 doses
    • Prodrug needs to be converted to 5-ASA
    • Onset of action ~ 2 weeks
    • Absorption very low and variable
    • Adverse effects
      – Headache, abdominal pain, GI discomfort
  – Dipentum® (osalazine)
    • 1.5-3 g/day divided into 2 doses
    • Prodrug needs to be converted to 5-ASA
    • Onset of action ~ 1 hour
    • Absorption is < 3%
    • Adverse effects
      – Dose-dependent headache, rash, pruritus, arthralgia
  – Apriso® (mesalamine)
    • 2-4.8 g/day divided into 3 doses
    • Available in several formulations
      – Enema (topical), tablet, and capsule
    • Onset of action depends on the specific product
      – Ranges from 2-10 hours
    • Absorption depends on route
      – Rectal varies
      – Tablet and capsule ~ 20-30%
    • Adverse effects
      – Headache, GI discomfort, pharyngitis
Topical Therapy

- In alternative to oral 5-ASA class
  - mesalamine topical
    - Suppository (Canasa®)
      - 1 g/day can be divided into 2 doses
    - Enema (Rowasa®)
      - 1-4 g/day can be divided into 2-3 doses
  - hydrocortisone topical
    - Foam 10% (Cortifoam®)
      - 1 applicatorful of 90 mg daily or BID X 2-3 weeks
    - Enema (Cortenema®)
      - 100 mg HS X 1-2 weeks
- Advantages
  - Quicker response
  - Less frequent dosing
  - Less systemic effects than oral

Thiopurines

- Available agents:
  - Azathioprine
    - Pro-drug: converts to 6-Mercaptopurine (6-MP)
    - 1.5-2.5 mg/kg/day
    - Faster onset of action
    - Absorption varies (better than 6-MP)
    - Adverse effects:
      - Malaise, N/V, diarrhea, leukopenia, myalgia
  - 6-MP
    - 1.5-2.5 mg/kg/day
    - Optimal affect occurs 3-6 months into therapy
    - Absorption ~ 50%
    - Adverse effects:
      - Malaise, rash, GI discomfort, bone marrow suppression

Thiopurines

- Mainly used to help wean patients off steroids
- Not suitable as monotherapy for remission
- MOA:
  - Acts as a false metabolite that is incorporated in the DNA and RNA pathway, eventually inhibiting their synthesis

Remicade® (Infliximab)

- MOA:
  - Chimeric monoclonal antibody that binds to human tumor necrosis factor alpha (TNFα) and inhibits TNFα activities, such as: induction of pro-inflammatory cytokines, acute phase reactants, and tissue degrading enzymes
Remicade® (Infliximab)

• **Induction dose:**
  - 5-10 mg/kg IV at 0, 2, 6 weeks
  - Intravenous formulation administered over 2 hours
  - Onset of action ~ 1-2 weeks
  - Must be screened for latent TB infection

• **Adverse effects**
  - Increased risk of infection, malignancies, hepatotoxicity
  - Serious infusion reactions
    - Decreased by slowing the rate of infusion (8 week dosing)
    - Premedication with antihistamines and corticosteroids
    - Prolonging infusion time

• **Landmark trials:** Active Ulcerative Colitis Trials 1 and 2 (ACT-1/ACT-2)
  - Multicenter, phase III, randomized, double-blind, placebo-controlled clinical trials
  - Evaluated the safety and efficacy of Remicade for the treatment of moderate-severe active UC
  - Total of 728 patients who were unresponsive to corticosteroids, 5-ASAs, or other immunosuppressants

• **Results:** By week 8, ~69% of patients had clinical response with Remicade 5 mg/kg and ~62% with Remicade 10 mg/kg

Simponi® (golimumab)

• **FDA Approved May 2013**

• **MOA:** Humanized monoclonal antibody that antagonizes TNFα

• **Dose:**
  - Induction: 200 mg Sub-Q at week 0, then 100 mg at week 2
  - Maintenance: 100 mg monthly
    - May increase to 200 mg monthly if needed

• **Adverse effects:** infection, URI, HTN, dizziness, skin rash, increased serum ALT, antibody development, injection site reactions

• **Half-life:** ~2 weeks

Entyvio® (vedolizumab)

• **FDA approved May 2014**

  - Adult patients with moderately to severely active UC or CD, who have inadequate response to TNFα blockers, immunomodulators, or corticosteroids

• **MOA:** Humanized monoclonal antibody that selectively antagonizes the α4β7 integrin receptors, preventing the interaction with mucosal addressin cell adhesion molecule (MAdCAM-1)
  - α4β7 integrin expressed on T-lymphocytes: Migration of memory T-lymphocytes across the endothelium into the inflamed GI parenchymal tissue
  - MAdCAM-1 mainly expressed on gut endothelial cells: critical role in homing T-lymphocytes to gut lymph tissue
**Entyvio® (vedolizumab)**

- **Dose:**
  - 300 mg IV infusion at 0, 2, and 6 weeks and then every 8 weeks
  - Discontinue therapy if no improvement by week 14
- **Adverse effects:** hypersensitivity reactions, infections, hepatotoxicity, progressive multifocal leukoencephalopathy
- **Half-life:** ~ 3-17 days
- **Patients should be brought up to date with all immunizations prior to initiating vedolizumab**
- **GEMINI 1/2 trials:** 14.5% remission at week 6 and 39% at week 54

**Medical Management:**

**Based on Disease Severity**

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**Mild - Moderate Distal Colitis**

- Both oral and topical therapies are available and effective
  - Topical mesalamine was shown to be more effective than oral aminosalicylates and the combination is superior to either therapies alone
- **Initial Treatment Options:**
  - Oral aminosalicylates
  - Topical mesalamine (enemas/suppositories)
  - Topical steroids
- **Refractory Treatment Options:**
  - Oral prednisone 40-60 mg/day
  - Infliximab induction regimen
Mild - Moderate Distal Colitis: Remission

- Oral 5-asa are effective in maintaining remission
- The combination of oral and topical mesalamine is more effective than either one alone
- Corticosteroids are not indicated for remission
- If remission fails on above agents then initiate,
  - Thiopurines
  - Infliximab

Mild - Moderate Distal Colitis: Active Disease

- Initiate oral 5-asa
  - First line is sulfasalazine
  - Target dose up to 4.8 g/day
  - +/- steroids if no response to oral 5-asa or combination with topical regimen
- If no response to the above regimens initiate
  - 6-MP or azathioprine
- If no response to the above regimen initiate
  - Infliximab

Mild - Moderate Extensive Colitis: Active Disease

- Dosing recommendations:
  - Mesalamine enema 2-4 g daily, every other day, or every 3rd day
  - Sulfasalazine 2 g/day
  - Olsalazine 1 g/day
  - Balsalazide 3-6 g/day
- Combination therapy
  - Mesalamine 1.6 g/day + mesalamine enema 6 g twice weekly
Mild-Moderate Extensive Colitis: Maintenance of Remission

- Oral 5-asa dosing regimens:
  - Sulfasalazine 2-4g/d
  - Olsalazine 1 g/day
  - Balsalazide 3-6 g/day
  - Mesalamine 1.6 g/day
- 6-mp and AZA can be used if uncontrolled with 5-asa
- Infliximab can be continued at 5mg/kg every 8 week
- Chronic corticosteroid use is not recommended for maintenance

Severe Colitis

- Treatment options:
  - Lacking systemic toxicity
    - Infliximab 5 mg/kg
    - Vedolizumab 300 mg IV infused over 30 minutes
  - Systemic toxicity requiring hospitalization
    - Hydrocortisone 300 mg/day
    - Methylprednisolone 60 mg/day
    - Other medications (5-ASA) should be held
    - Consider seeking surgical guidance

Severe Colitis

- Refractory to oral steroids, oral 5-ASA, and topical medications
- May be initially treated with infliximab, if the systemic toxicity does not require hospitalization
- If systemic toxicity, first line treatment is a course of high-dose intravenous steroids

Severe Colitis

- Inadequate response to IV steroids after at least 3 days
  - Cyclosporine is the last treatment option
    - 2-4 mg/kg/day continuously infused over 24 hours
    - Onset of action ~ 2-6 hours
  - Surgery
    - Total or subtotal colectomy
- Fulminant Colitis
  - Requires the same treatment
  - Re-evaluation after IV steroid use occurs quicker
Surgical Intervention

Drugs in the Pipeline

- Etrolizumab: Phase III
  - Anti-adhesion molecule that selectively binds to α4β7 and αEβ7 integrins (similar to natalizumab and vedolizumab)
  - EUCALYPTUS trial: clinical remission was observed in 21% of patients
- Ozanimod: Phase II
  - Oral immunomodulator targeting sphingosine 1-phosphate receptor (S1P)
    - S1P: sequesters T-cells, interfering with the ability of the cells to recognize their way back out of the lymph node
    - TOUCHSTONE Study: 56.7% remission rate by week 8

Drugs in the Pipeline

- Mongersen: An oral 21-base single-stranded anti-sense oligonucleotide
- MOA: Facilitates degradation of the human SMAD7 mRNA, via antisense mechanisms
  - SMAD7: inhibits transforming growth factor β1 (TGFβ1)
  - TGFβ1: inhibits T-cell proliferation, differentiation, and macrophage activation (reduced proinflammatory cytokines)
- Modified release tablet designed to deliver drug into the lumen of the ileum/right colon
- Phase II trials show induced remission rates between 55 and 65%
Introduction
• CD is a chronic inflammatory disorder affecting the gastrointestinal (GI) tract
  – Multisystem disorder with specific clinical and pathological changes
• Most commonly diagnosed between the 2nd and 3rd decade of life
• Incidence in the US is approximately 5 out of every 100,000 people
  – Prevalence is approximately 50 out of every 100,000 people
• Direct medical cost is ~ $2 billion dollars annually

Crohn’s Disease (CD)

Signs/ Symptoms and Diagnosis
• Nocturnal diarrhea
• Abdominal pain
• Weight loss
• Fever
• Rectal bleeding
• Extraintestinal features:
  – Inflammation of the eyes, skin, or joints
  – Children: fever, failure of growth, delayed development of 2nd sex characteristics

Crohn’s Disease
Ulcerative Colitis
## Diagnostic Tools

- Similar to UC, other conditions must be ruled out through stool testing and endoscopic testing
- **Endoscopy**
  - Main tool used to confirm CD diagnosis
  - Findings: Focal, asymmetric, transmural, or granulomatous tissue
- **Imaging Studies**
  - MRI and CT have been used to confirm UC diagnosis
  - Help delineate and discriminate intra-abdominal masses/abscess (IAI)

## Measuring Disease Severity

- **Lack of a “gold standard” approach**
- **Assessment based on:**
  - Location, severity, GI complications, and quality of life
- **European Crohn’s and Colitis Organization (ECCO) developed a grading scale**
  - Used in multiple studies
  - Practitioners are constantly working on definitions

## Disease Severity

- **Mild-moderate**
  - Ambulatory patients
  - Tolerate PO diet
  - Lack of systemic toxicity, abdominal tenderness, intestinal obstruction, > 10% weight loss
- **Moderate – Severe**
  - Failed treatment for mild-moderate disease
  - Prominent symptoms
    - Fever
    - Significant weight loss
    - N/V
    - Anemia
- **Severe- Fulminant**
  - Persistent symptoms despite available therapies
    - Corticosteroids and/or biologic agents
    - High fevers
    - Persistent vomiting
    - Evidence of abscess or intestinal obstruction
    - Cachexia
Goals of Treatment

• Active Disease
  – Treatment should be continued to the point of symptomatic remission
  – Usually 2-4 weeks; max 12-16 weeks
  – Once remission achieved; maintenance therapy should be initiated

• Persistent active disease
  – Should progress from treatment of mild-moderate disease to moderate-severe and so on and so forth

Mild-Moderate Active Disease

• Ileal, ileocolonic, or colonic locations
  – Oral 5-asa
    • Mesalamine 3.2-4 g/day
    • Sulfasalazine 3-6 g/day
  – Antibiotic (ABX)
    • Metronidazole 10-20 mg/kg/day
    • Ciprofloxacin 1 g/day
  – Steroid
    • Budesonide 9 mg/day

Medical Management: Base on Disease Severity

Mild-Moderate Active Disease

• If associated with infection or abscess should be treated appropriately
  – ABX and/or incision and drainage (I&D)

• Steroids
  – Prednisone 40-60 mg/day
  – Ipred for symptom resolution (7-28 days)

• Thiopurines
  – 6-MP 1-1.5 mg/kg/day
  – AZA 2-3 mg/kg/day

• Integrin antagonists
  – Vedolizumab 300 mg at 0, 2, and 6 weeks

• Anti-TNF monoclonal antibodies
  – Adalimumab 160 mg, followed by 80 mg on week 2
  – Certolizumab 400 mg
  – Natalizumab 300 mg at weeks 0, 4, and 8
  – Infliximab 5-10 mg/kg at weeks 0, 2, and 6

  * Last line after others failed
  * Can be used in combo with AZA

Moderate-Severe Active Disease

• If associated with infection or abscess should be treated appropriately
  – ABX and/or incision and drainage (I&D)

• Steroids
  – Prednisone 40-60 mg/day

• Thiopurines
  – 6-MP 1-1.5 mg/kg/day
  – AZA 2-3 mg/kg/day

• Integrin antagonists
  – Vedolizumab 300 mg at 0, 2, and 6 weeks

• Anti-TNF monoclonal antibodies
  – Adalimumab 160 mg, followed by 80 mg on week 2
  – Certolizumab 400 mg
  – Natalizumab 300 mg at weeks 0, 4, and 8
  – Infliximab 5-10 mg/kg at weeks 0, 2, and 6

  * Last line after others failed
  * Can be used in combo with AZA
Tissue Necrosis Factor-α (TNF-α) Antagonists

- Monoclonal antibodies
- Binds to, and antagonizes TNF-α, preventing cytokine-driven inflammatory processes
- Agents:
  - Remicade® (infliximab)
    - Previously stated
  - Humira® (adalimumab)
    - 160mg Sub-Q (four 40mg injections on day 1 or two 40mg injections for 2 days)
    - Then 80 mg given 2 weeks later (day 15)
    - Bioavailability: 64%
    - Half-life: ~2 weeks
    - Adverse effects (>10%): Headache, skin rash, antibody development, injection site reactions, upper respiratory infection, increased creatine phosphokinase

Tissue Necrosis Factor-α (TNF-α) Antagonists

- Cimzia® (certolizumab pegol)
  - 400mg Sub-Q on weeks 0, 2, and 4
  - Bioavailability: ~80%
  - Half-life: ~14 days
  - Adverse effects (>10%): Nausea, antibody development, infection, and upper respiratory tract infection

Tysabri® (natalizumab)

- MOA: IgG4 humanized monoclonal antibody that antagonizes α4 integrin receptors
  - Gut (MAdCAM-1) and vasculature (VCAM-1)
- 300mg IV over 1 hour every 4 weeks, discontinue if benefit not observed within 12 weeks
- Half-life: 3-17 days
- Adverse effects (>10%): headache, fatigue, depression, rash, nausea, gastroenteritis, abdominal discomfort, UTI, arthralgia, extremity pain, back pain, URI, influenza, flu-like syndrome, progressive multi-focal leukoencephalopathy

Severe-Fulminant Active Disease

- Persistent symptoms in spite of adequate therapy and oral steroid use
- Intravenous corticosteroids
  - Equivalent dose of prednisone 40-60mg/daily as a continuous infusion
- Intravenous Cyclosporine
  - Used if no improvement with IV steroids
  - 2-4 mg/kg as a continuous infusion
**Maintenance Therapy**

• Oral 5-asa have not proven to be effective
• Budesonide 6mg/d does not provide significant benefits after 6 months
• Optimal agents
  – Anti-TNF / Anti-integrin monoclonal antibodies
    • Infliximab – 5mg/kg every 8 weeks
    • Adalimumab – 40mg SQ every other week
    • Certolizumab – 400mg SQ every 4 weeks
    • Natalizumab – 300mg IV every 4 weeks
    • Vedolizumab – 300 mg every 8 weeks

**Surgical Management**

• GI resections are indicated if remission is not obtained with available agents, intractable hemorrhage, perforation, persistent/recurrent obstruction, abscess, and/or malignancy
• Primary objective of this “incurable” condition is to optimize patient’s quality of life
  – Surgery should not be considered as last resort or as a treatment failure
  – Should be performed when deemed appropriate

**Questions**
References


