How do I choose amongst medicines for inflammatory bowel disease

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Overview of IBD Pathogenesis

Bacterial Products

Normal Gut
Mildly Inflamed

Moderately Acutely Inflamed

Failure to Downregulate

Downregulated

Chronic Inflammation
= IBD

Normal Gut
ULCERATIVE COLITIS AND CROHN'S DISEASE

- Diffuse mucosal inflammation limited to colon
- Affects rectum
- May involve all or part of rest of colon

- Patchy transmural inflammation
- May affect any part of GI tract
Symptoms of inflammatory bowel disease

- Diarrhea
- Abdominal pain and tenderness
- Loss of appetite and weight
- Fever
- Fatigue
- Rectal bleeding
- Perianal disease (CD)
- Stunted growth in children (CD)
DIFFERENTIAL DIAGNOSIS OF IBD AND IBS

Clinical features

- Anemia, ↑ platelets, ↑ sed. rate, ↓ albumin
- Weight loss, fever
- Perianal disease
- Bloody stools, tenesmus
- Fecal WBC, occult blood

IBD

IBS
Diagnosis of IBD

History and Physical

Genetic testing

Radiology

Pathology

Serologic testing

IBD
Normal intestinal function

- Nutrient absorption
- Net secretion of fluid
- Net absorption of fluid
- Reservoir function
Abnormal intestinal function in IBD

- Obstruction
- Pain
- Abscess
- Bleeding
- Urgency
- Cramping
- Diarrhea (multifactorial)
Normal colon
Crohn’s Colitis

Transverse (edema, granularity)

Descending (normal)

Sigmoid (purulent, ulcerated)

Rectum (aphthous ulcers)
Crohn’s colitis
Crohn’s disease ileitis
Upper tract Crohn’s disease
Perianal fistula
Perianal fistulae
Moderate Ulcerative Colitis

Transverse (normal)

Descending (↑vascular markings)

Sigmoid (erythema, granularity)

Rectum (ulcerated, purulent)
Severe Ulcerative Colitis
Severe Ulcerative Colitis

Recto-Sigmoid
Indeterminate colitis
Therapeutic Pyramid for IBD

**Induction of Remission/Active Disease**
- 5-ASA
- Infliximab
- Tacrolimus
- Cyclosporine
- Experimental therapies
- anti-CD3

**Maintenance of Remission**
- Experimental
- Infliximab
- Methotrexate (CD)
- 6-MP/AZA
- 5-ASA
- 6-MP/AZA
5-ASA Release Sites

Stomach
- Pentasa®
- Asacol®
- Azulfidine®

Small Intestine
- Lialda®
- Dipentum®
- Colazal®

Large Intestine
- Mesalamine in microgranules
- Mesalamine w/ eudragit-S
- Azo bond
- Mesalamine with MMX delivery
- Rowasa®
- Canasa®
Aminosalicylate Dosing for Reduction of Signs/Symptoms

Dose-Response without Intolerance

% Response

Schroeder, Tremaine, Ilstrup, 1997; Hanauer, 1993; Sninsky, 1991
ASCEND II
Treatment Success at Weeks 3 & 6

Treatment Success Rates at Weeks 3
*Moderate Population*

<table>
<thead>
<tr>
<th>% of Patients Improved</th>
<th>2.4 g/day</th>
<th>4.8 g/day</th>
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<tbody>
<tr>
<td>3 weeks</td>
<td>52%</td>
<td>61%</td>
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<tr>
<td>6 weeks</td>
<td>59%</td>
<td>72%</td>
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</table>
Modulating the Immune System

Trafficking
- Antisense ICAM
- Anti-α4β7
- Anti-α4
- Corticosteroids

Proliferation
- Cyclosporine
- Tacrolimus
- Anti-IL-2 receptor
- IL-2
- IL-2
- IL-2
- IL-2
- 6-MP/AZA
- Methotrexate
- Anti-CD3

T-Cell Regulation
- TNF-α
- IL-1β
- IL-12 / IL-18
- IFN-γ
- IL-4 / IL-13
- IL-1Ra
- TGFβ
- IL-10
- (Corticosteroids)
ENTOCORT EC Capsules
Release and Absorption

Majority of ENTOCORT EC delivered and absorbed in the ileum and throughout the colon.

10%-20% Systemic circulation

Capule

Ileum

Cecum
ENTOCORT EC Capsules Effective for Inducing Remission*

*Clinical remission is defined as a CDAI score of 150 or less after 8 weeks of treatment.

**P < .001 vs placebo

†P = .009 vs placebo

Treatment of Colitis by Inhibition of $\text{Th}_1$

- Colitis
- Treatment
  - Anti-IL-12
  - Anti-TNF$_{\alpha}$
  - Anti-IFN$_{\gamma}$
  - IL-10
- Attenuated/ No Colitis
Monoclonal Antibodies, Fusion Proteins and Fc-Free Fab’ Fragments Against TNF

- **Chimeric monoclonal antibody**
  - Infliximab (Remicade®)
  - Adalimumab (Humira®)

- **Human monoclonal antibody**
  - Etanercept (Enbrel®)

- **Human recombinant receptor/Fc fusion protein**
  - Receptor
  - Constant 2
  - Constant 3

- **Humanized Fc-Free Fab’ fragment**
  - Certolizumab pegol (Cimzia®)
Clinical Response and Remission at Week 4: Anti–TNF-α Agents

Maintenance of remission in CD: are all anti-TNF antagonists created equal?

Week 26–30

<table>
<thead>
<tr>
<th>Condition</th>
<th>Infliximab 5 mg/kg (ACCENT I)</th>
<th>Adalimumab 40 mg EOW (CHARM)</th>
<th>Certolizumab 400 mg 4-weekly (PRECISE 2)</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>Remission (CDAI&lt;150)</td>
<td>21</td>
<td>17</td>
<td>29</td>
<td>48</td>
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<tr>
<td>Response (Δ100)</td>
<td>51</td>
<td>52</td>
<td>63</td>
<td>44</td>
</tr>
<tr>
<td>Reduction (≥ 70 pts and ≥ 25% in CDAI)</td>
<td>27</td>
<td>26</td>
<td>36</td>
<td>22</td>
</tr>
<tr>
<td>N</td>
<td>113</td>
<td>172</td>
<td>215</td>
<td>215</td>
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</table>
Safety: Class effects

- Tuberculosis
- Intracellular pathogens: Pneumocystis, atypical mycobacteria, listeriosis, legionella, coccidiomycosis, histoplasmosis, and aspergillus
- Risk of infection
- Lymphoma: unclear risk
- Demyelinating disorders
Managing Nutrition in IBD

- Malnutrition can occur in IBD
  - Decreased intake of food
    - Symptoms
    - Overly zealous restriction
  - Decreased absorption of nutrients
    - Active disease, small intestine
  - Increased needs for calories and protein
- Professional nutritional assessment
- Tailor diet to individual needs & preferences
- Dietary supplements
Surgery in IBD

**Ulcerative Colitis**
- Surgery (colectomy, removal of colon)
- Colectomy & ileostomy
- Colectomy & ileo-anal anastomosis (J-pouch)

**Crohn’s Disease**
- Surgery does not cure
- Disease recurs after a resection
  - Less after an “ostomy”
- Resection of inflamed segments to treat complications or “refractory” disease
Ulcerative Colitis

Indications for Surgery

- Failure to control severe attacks or toxic megacolon
- Acute complications
- Chronic symptoms despite medical therapy
- Medication side effects without disease control
- Dysplasia (pre-cancer) or Cancer
Crohn’s Disease
Indications for Surgery

- Obstructing strictures
- Complicating fistula
- Peri-anal abscess
- Toxic megacolon
- Localized, unresponsive disease
Colorectal Cancer Risks in IBD

• Compared to general population
  • Risk is 10-20 times higher
  • Occurs at younger age

• Risk is same for UC and CD according to:
  • How much of colon is affected
  • How long the disease is present
  • Severity of disease activity
  • If patient has liver disease (PSC)
Preventing Colon Cancer in IBD

- Compliance with maintenance medications
  - 5-ASA agents
- Regular follow-up and surveillance colonoscopies
  - Every 1-2 years after 10 years
  - Every year after 20 years
- Colectomy (removal of colon) if:
  - Dysplasia (confirmed pre-cancerous changes)
  - Unwilling to continue surveillance examinations
Future of IBD Diagnosis and Management: the Roadmap

- Molecular classification
- Genetic diagnosis and susceptibility determination
- Presymptomatic screening and prevention
- Individualized therapies, targeted biologic therapies
- Reduction/elimination of complications
- Prevention?