Modern Management of Inflammatory Bowel Disease
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Medical College of Wisconsin

Objectives
- Review of Crohn’s Disease and UC
- Approach to Therapy
- Summarize the benefits of drug therapy options for IBD.
- Review the side effects of drug therapy options for IBD.
- Identify the risks associated with drug therapy options for IBD.
- Discuss treatment philosophies concerning drug therapy.

Overview
- Total number of cases
  - 1 to 1.5 million cases estimated in United States
  - Ulcerative Colitis: 50%
  - Crohn’s disease: 50%
- Number of new cases annually
  - 10 new cases per 100,000 people per year
  - Prevalence ~200 cases per 100,000 in the West

11/4/2014
Ulcerative Colitis

UCERATIVE COLITIS
- Continuous inflammation
- Colon only
- Superficial inflammation
- Variable involvement
- Risk of cancer

Clinical Presentation of Ulcerative Colitis
- Diarrhea, typically bloody and with mucus
- Urgency and incontinence
- Tenesmus (rectal “dry heaves”)
- Loss of appetite and weight
- Fever and sepsis
- Abdominal pain and tenderness
- Children: growth and developmental failure


A. Mild Colitis with loss of vascular pattern
B. Severe Colitis – spontaneous bleeding and friability
A. Erythematous, friable, loss of vascular pattern – also notice continuous and circumferential pattern
B. Pseudo polyps
C. Lots of Pseudo polyps

**UC: Natural History**

![Graph showing percentage of patients with disease activity, in remission, or having colectomy performed each year after diagnosis](image)

**Crohn’s Disease**

- Patchy inflammation
- Mouth to anus involvement
- Full-thickness inflammation
- Variable involvement
- “Cobblestone” appearance
- Fistulae
- Strictures

Clinical Presentation of Crohn’s Disease

- PEDIATRIC
  - Abdominal pain
  - Diarrhea
  - Weight loss
  - Anorexia
  - Vomiting
  - Rectal bleeding
  - Stunted growth
  - FEVERS

- ADULT
  - Similar presentation
  - Growth and development issues less apparent
  - Often had silent disease as child/teen


Skip Lesions

Cobblestoning

Natural History of Crohn’s Disease

What happens if we do nothing or under-treat your Crohn’s disease?
Inflammatory Activity and Progression of Damage in a Theoretical Patient with CD

- CDAI, Crohn’s Disease Activity Index
- CDEIS, Crohn’s disease endoscopic index of severity
- CRP, c-reactive protein

Crohn’s Disease: 1960s Historical Perspective

- Limited treatment options: sulfasalazine, prednisone
- No treatment algorithm, limited options available
- Irreversible complications
IBD is for LIFE and we don’t cure it.

What therapy gives us the BEST chance of alternating the natural history of their disease?

This is the real question.
Goals of Management of IBD

- Induce remission
  - Absence of symptoms, feeling “well”
  - Absence of objective inflammation
- Maintain remission
  - 95% of patients require maintenance therapies
  - Maintenance occurs after successful induction
- Avoid Surgery
  - Enhance quality of life
  - Avoid complications
    - Hospitalization, abscess, infection, etc.

AVOID THIS!!!!!!

Medications used for IBD

- Mesalamines
  - Sulfasalazine, Asacol, Lialda, Canasa
- Immunomodulators
  - Azathioprine, 6 Mercaptopurine, Methotrexate
- Corticosteroids
  - Prednisone, prednisolone, etc.
Monotherapy with Azathioprine?

Azathioprine for newly diagnosed Crohn's disease
Top Down Therapy With Azathioprine + Prednisone Versus Prednisone In Adults With Newly Diagnosed Crohn’s Disease

Panes J. Gastroenterology 2013

Sustained steroid free remission
Survival free of relapse

Week 28  Week 52  Week 70

Mono-therapy with anti TNFs?

Durability of Infliximab for CD

- 50% of CD patients have discontinued infliximab by 6 years of maintenance therapy (n=183)

Factors in anti-TNF failure

- Low Serum Levels of Drug
- Immunogenicity (HACA/ATI/ADA)
- Loss of mechanism
- Smoking status
- Young age
- Male gender
- Duration of disease
- Prior TNF therapy

What can be done to modify these factors?

- Cannot modify disease duration, prior TNF therapy, or loss of mechanism
- You CAN encourage smoking cessation
  - You CAN bang your head against the wall too.
- Can you do something about the drug levels and immunogenicity?
  - Yes!
What can be done to modify these factors?

#1 Avoid Episodic Dosing

Effect Episodic Dosing on Long-term Performance of Infliximab Maintenance:

- 40 patients with prior irregular dosing
- 61 patients with scheduled maintenance

ACCENT I: Antibodies to infliximab reduced by induction and maintenance
What can be done to modify these factors?

#2 Concomitant Immunosuppression

ACCENT I: Antibodies to infliximab reduced by induction and maintenance

<table>
<thead>
<tr>
<th>Patients antibody [%] (%)</th>
<th>No immunomodulators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Episodic strategy</td>
<td>38</td>
</tr>
<tr>
<td>Maintenance Q8W 5 mg/kg</td>
<td>11</td>
</tr>
<tr>
<td>Maintenance Q8W 10 mg/kg</td>
<td>8</td>
</tr>
</tbody>
</table>

Manaseri et al, Lancet 2002; 359: 1561

ACCENT I: Antibodies to infliximab reduced further by induction and maintenance + Immunomodulator therapy

<table>
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<tr>
<th>Patients antibody [%] (%)</th>
<th>No immunomodulators</th>
<th>With immunomodulators</th>
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<td>Episodic strategy</td>
<td>38</td>
<td>16</td>
</tr>
<tr>
<td>Maintenance Q8W 5 mg/kg</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>Maintenance Q8W 10 mg/kg</td>
<td>8</td>
<td>4</td>
</tr>
</tbody>
</table>

Manaseri et al, Lancet 2002; 359: 1561
Methotrexate Works Too

So does combo therapy work?

CHARM: Effect of concomitant immunosuppressant use on remission at weeks 26 and 56 randomized responders

There was no significant difference between the response of patients receiving concomitant immunosuppressants vs those who were not at either dose of adalimumab and at either time point (Treslow Day).

IMM: immunomodulator
Hamauer et al, Presented at ACG 2006, Las Vegas
But are we looking at the wrong patients?

Why did these studies not detect a difference?

Patient Population

- ACCENT, CHARM, and PRECiSE
  - Not powered to detect differences
  - Longer duration of disease

Long-term evolution of disease behavior in Crohn’s disease

Cumulative probability (%)

<table>
<thead>
<tr>
<th>Patients at risk:</th>
<th>552</th>
<th>228</th>
<th>95</th>
<th>37</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cosses et al, Inflamm Bowel Dis 2002; 8: 244-50
SONIC Trial

- Moderate to Severe Crohn's Disease
- Less than 2 years of disease
- No prior immunomodulator or biologic exposure
- Randomized to 3 groups:
  1. Azathioprine + Infliximab placebo
  2. Infliximab + Azathioprine placebo
  3. Infliximab + Azathioprine (combo therapy)
So EVERYONE gets combo therapy, right?

High risk predictors

- High risk anatomy
  - Foregut disease
  - Perianal disease
  - Fistulizing disease
  - Young age at Dx
  - Second TNF
  - Diagnosis at time of initial surgery

- Extra-intestinal Manifestations
  - Severe activity
  - Weight loss, Low albumin, anemia, etc
  - Deep ulcers on endoscopy
Low risk predictors

- Mild inflammatory disease.
- Responders to mesalamine.
- No steroids.
- Symptoms but no mucosal disease
  - IBS
  - Other disorders (Cdiff, infection, etc)

SONIC Subgroup Analysis

93/415 22% had no mucosal lesions upon entry into the study!
Staging Disease Activity
- About 30% of patients endoscopic findings do not correlate with labs or clinical picture.
  - ~15% no objective disease, big complainers
    - (hard to deal with)
  - ~15% with objective disease, don’t complain
    - (hard to treat)
- This is why we scope patients periodically to assess the effectiveness of our therapy.

Subclinical Inflammation
- Patients with endoscopic inflammation, but with no symptoms.
  - Often don’t present until a complication develops.
  - Usually under treated.
- This is the most important reason to scope patients regularly
  - Interval is not clear
  - My practice is every 1-3 years based on many factors
- Not included in clinical trials so use caution with applying clinical trial data.

Other causes of symptoms
- Infections, Infections, Infections
- Fibrostenotic disease
- Post-Inflammatory IBS
  - 40-50% will have IBS like symptoms
  - Higher post-operatively
- Psychiatric illnesses
Other causes of symptoms
- Narcotic abuse/withdrawal
- Adrenal insufficiency
- Autonomic dysfunction
- SBBO
- Constipation

Bottom Line
- Make sure your patient has active disease before making changes to therapy!

Safety
### Table 1. Association of immunosuppressive Medication with Opportunistic Infection

<table>
<thead>
<tr>
<th>Medication</th>
<th>Cases (n=150)</th>
<th>Controls (n=200)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corticosteroids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CsA/Puri</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infliximab</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclosporine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroids + Infliximab + Cyclosporine</td>
<td>5 (33%)</td>
<td>2 (1.2%)</td>
<td>6.2 (1.6-38)</td>
</tr>
</tbody>
</table>

**Note:**
- Cases: n = 150
- Controls: n = 200

### Steroids are bad!!!

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#### Steroids are bad!!!

### Serious infections and anti-TNF therapies: The problem with confounding factors

**TREAT registry data as of August 2005**

(n=253 with 15,000 patient-years follow-up)

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Cox regression analysis</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current use of infliximab</td>
<td>1.40</td>
<td>0.95-2.07</td>
</tr>
<tr>
<td>Current use of cyclosporine</td>
<td>2.01</td>
<td>1.40-2.90</td>
</tr>
<tr>
<td>Current use of nonsteroidal analgesics</td>
<td>2.72</td>
<td>1.87-3.96</td>
</tr>
</tbody>
</table>

*Serious infections were determined within 3 months of an infliximab infusion (p<0.0001)

**Lichtenstein et al. Gastroenterology, 2008; 4: 421-30**

### SONIC summary of adverse events through Week 50: All randomized patients

<table>
<thead>
<tr>
<th>Medication</th>
<th>AZA + Placebo (n=161)</th>
<th>IFX + Placebo (n=163)</th>
<th>IFX + AZA (n=179)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with ≥1 AE, n (%)</td>
<td>144 (89.4%)</td>
<td>145 (89.0%)</td>
<td>161 (89.9%)</td>
</tr>
<tr>
<td>Patients with ≥1 SAE, n (%)</td>
<td>43 (26.7%)</td>
<td>39 (23.9%)</td>
<td>27 (15.1%)</td>
</tr>
<tr>
<td>Serious infections</td>
<td>9 (5.6%)</td>
<td>8 (4.9%)</td>
<td>7 (3.9%)</td>
</tr>
</tbody>
</table>

**Colombel et al., N Engl J Med 2010; 362: 735-85**
Steroid Side Effects

- Psychiatric
  - Psychosis
  - Depression
  - Suicide
- Infection
- Metabolic
  - Weight gain
  - Diabetes
  - HTN
- Acne
- Moon faces
- Osteoporosis
- OSTEONECROSIS of the hip

AGA, ACG, CCFA Guidelines for DEXA Screening

- Lifelong exposure of >3 months prednisone
- Post-menopausal
- Other osteoporosis risk factors
  - Post menopausal women at greatest risk

Osteonecrosis (Avascular Necrosis)

- Related (almost always) to high cumulative steroid dose
- Mt. Sinai Series----23 patients with IBD and osteonecrosis
  - Mean duration usage = 25 months
  - Mean maximum daily dose = 61 mg
  - Mean daily dose = 21 mg
Number Needed to Harm

<table>
<thead>
<tr>
<th>Males Only</th>
<th>15-19 y.o. M (per 10⁵)</th>
<th>20-24 y.o. M (per 10⁵)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphoma other than HSTCL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annual incidence NHL + HD USA</td>
<td>5.2</td>
<td>7.0</td>
</tr>
<tr>
<td>Annual incidence NHL + HD with thiopurines (4%)</td>
<td>20.8</td>
<td>28.0</td>
</tr>
<tr>
<td>Annual mortality from lymphoma without thiopurines*</td>
<td>1.3</td>
<td>1.75</td>
</tr>
<tr>
<td>Annual mortality from lymphoma with thiopurines*</td>
<td>5.2</td>
<td>7.0</td>
</tr>
<tr>
<td>Excess deaths from thiopurine induced lymphoma</td>
<td>3.9</td>
<td>5.25</td>
</tr>
<tr>
<td>NNT to cause one death / year</td>
<td>25,641</td>
<td>19,074</td>
</tr>
</tbody>
</table>

5 year survival for NHL with thiopurines is about 76 to 93% following chemotherapy.

* 5 year survival = 68% for NHL, 85% for HD, estimated at 75% for this example

Hepatosplenic T-cell Lymphoma: Should it effect choice of immune modulator?

- Among patients on concomitant thiopurine and anti-TNF therapies, the absolute risk is under 1:22,000
- For patients < 35y
  - Risk of thiopurines monotherapy: 1:7,404
  - Risk of combination therapy: 1:3,534

Anti-TNF CONTRAINDICATIONS

- Active bacterial infections or bacterial infections requiring antibiotic therapy
- Active tuberculosis (TB) or untreated latent TB
- Active herpes zoster infection
- Active life-threatening fungal infections
- Severe bacterial or viral upper respiratory tract infections
- Non-healed infected skin ulcers
- Acute hepatitis B or C infection
- Chronic hepatitis B or C infection (treated or untreated) with significant liver injury, defined as chronic Child-Pugh classes B or C

The American College of Rheumatology
Active Infections:
When to hold anti-TNF therapy

- Remember these patients still have remicade or other immunosuppressive drug on board.
- Infliximab level at dosing
- Most of our immunosuppressive drugs take weeks, months to clear.
- Holding doesn’t really make a big difference for minor infections.
- Hold for serious infections or suspicion of serious infections.

Vaccines

- Initial Anti TNF therapy should be held for 4 weeks following any live vaccine.
- No recommendations on household contact and anti-TNF therapy
  - Either vaccinations or active disease
  - Best course is good hand washing
  - Avoid intimate contact (kissing, etc.)
  - No clear role for prophylactic therapy but some do it for Varicella exposure.
Vaccinations

- Patients on anti TNF therapy should be vaccinated against age appropriate therapy.
- Preferably before anti TNF initiation
- TNF lower response to vaccines
- Hepatitis B
- Pneumovax every 5 years
- HPV/Gardasil
- DTap every 10 years
- Influenza yearly
- Meningococcal for appropriate population
  - Students in dorms

Monitoring for side effects

Monitor Medical Therapy: Mesalamines

- Nephrotoxicity:
  - Measurement of BUN/Cr at baseline
- FDA: “Periodic” measurement of BUN/Cr
  - Reduce dose if baseline renal function impaired
  - Reduce or eliminate if BUN/Cr progressively rise
Azathioprine, TPMT and the FDA: PDR 2012

- "TPMT genotyping or phenotyping can help identify patients who are at an increased risk for developing azathioprine toxicity."
- "Patients with low or absent TPMT activity are at an increased risk of developing severe, life-threatening myelotoxicity if receiving conventional doses of azathioprine."

Monitor Medical Therapy: 6-MP/AZA

- Check baseline TPMT
- Bone marrow suppression: Check CBC, weekly or bi-weekly for 1 month then monthly for 3 months then every 3 months
- Hepatotoxicity—monitor LFTs as above
- Lymphoma

Prior to TNF Initiation

- Absolute Must
  - TB testing
  - HBV status
- Strongly recommended
  - HCV status
  - Fungal testing (regional specific)
  - HIV (GI only, weak)
Monitor Medical Therapy: Anti-TNF drugs

- Infection
  - TB yearly
- Hepatitis B, or other hepatotoxity
- Infusion reaction
  - Anaphylaxis
- Neurotoxicity
  - MS, optic neuritis
  - Seizures
  - Diverse list of neurotoxicity
- Lymphoma

New Therapies

Vedolizumab: A Humanized, Monoclonal Antibody (mAb) Against α4β7 Integrins

- Targets only α4β7 integrin
- IV infusion over 30 – 60 minutes
- Dosed at 0, 2 and 6 weeks then every 8 week
- Fixed dose of 300 mg
**Blockade of Adhesion Molecules: Vedolizumab**

**Initial Ulcerative Colitis Study**
- Week 6 Endpoint

**Initial Crohn’s Disease Study**
- Week 8 Endpoint

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**Side effects/Safety**
- No requirement to test for TB prior to initiation
- No need to test for JC virus (cause of PML)
- Possible mild elevations in LFTs
- Increased incidence of nasopharyngitis most common side effect.
- No specific monitoring is recommended by FDA other than monitor for infections and periodic LFTs

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**Vedolizumab**
- Approved for UC and CD patients
- Patients do NOT have to have failed anti-TNF therapy
- Effective for TNF naïve and exposed patients.
- When to use?
  - New diagnosis
  - Failing anti-TNFs
  - Basically anytime you are considering immunosuppressive therapy.
Summary
What we know and what we need to know.

What we know
- Ulcerative Colitis and Crohn’s disease are life long chronic diseases
  - Progressive in most patients.
  - Frequently require surgery
  - Can result in disfiguring and disabling complications.
  - Proper disease evaluation and monitoring is essential to good care.
What we know

- Regular dosing of biologic and concomitant immunomodulators
  - Avoids immunogenicity
  - Boosts drug levels
  - Improves mucosal healing rates
- Early aggressive therapy CAN change the natural history and minimize steroid exposure.
- Combination therapy safe in short term.

What we know

- Document active inflammation before initiating anti-TNF
- Treat active infection before starting anti-TNF
- Active drug monitoring prevents serious side effects
- Prevent preventable infections with vaccination

IBD is for life.