Optimizing Treatment Strategies in the Management of Inflammatory Bowel Disease (IBD)

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Disclosures  April 2013

Within the past 24 months, I have had financial relationships with commercial entities and the content of my presentation includes discussion of off-label/investigative use of medicine(s), medical devices, or procedures.

Lecturer: Abbott, Salix, Santarus, Shire

Consultant: Abbott, Elan Pharmaceuticals, Janssen (Johnson & Johnson), Prometheus Laboratories, Salix Pharmaceuticals, Santarus, Sanofi-Aventis, Santarus,UCB, Warner Chilcott.
“IBD”: Inflammatory Bowel Disease

Important: Disclaimer

- “IBD” = Inflammatory Bowel Disease
- “IBS” = Irritable Bowel Syndrome

\[ \text{IBD} \neq \text{IBS} \]
IBD: Chronic Inflammation
An Imbalance!

An imbalance between pro- and anti-inflammatory Events.

Normal Intestine
Vs. Intestine With IBD

Environmental triggers (infection, bacterial products)

Fail to down-regulate

Moderately inflamed

Chronic uncontrolled inflammation = IBD

Down-regulate

Normal gut controlled inflammation

Normal gut controlled inflammation
Another definition:

“Remission”
• The absence of disease or the impact upon disease upon the patient.
• Expectations change as therapies improve!

Remission = Perfection
(to the extent that non-perfection is due to active disease!)

Treatment Goals in IBD
1. Induce Remission.
2. Maintain Remission.
3. Mucosal healing.
4. Prevent Complications
   – Disease Related
   – Therapy Related
5. Limit Surgery
6. Improve Quality of Life
Current “Therapeutic Pyramids”

Crohn’s Disease

Severe

Surgery

Anti-TNF*

MTX

AZA/6-MP

Budesonide*

Systemic Steroids

Anti-TNF*

Natalizumab*

Moderate

Budesonide*

Antibiotics

Aminosalicylates

Mild

Budesonide*

Aminosalicylates*

Ulcerative Colitis

Severe

Surgery

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Anti-TNF*

Natalizumab*

Mild

Budesonide*

Aminosalicylates*

* FDA Approved

1-2 Years From Now:
Potential Therapeutic Pyramids

Crohn’s Disease

Severe

Surgery

Anti-TNF*

Anti-Adhesion

MTX

AZA/6-MP

Budesonide*

Systemic Steroids

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Systemic Steroids

Anti-TNF*

Mild

Budesonide*

Antibiotics

Aminosalicylates

Helminth Ova

? Fecal Transplant

Ulcerative Colitis

Severe

Surgery

Anti-TNF*

AZA/6-MP

Budesonide*

Systemic Steroids

Anti-TNF*

Mild

Budesonide*

Aminosalicylates*

* FDA Approved
1-2 Years From Now:
Potential Therapeutic Pyramids
Crohn’s Disease | Ulcerative Colitis
--- | ---
Severe
- Surgery
- Anti-TNF*
- Anti-Adhesion
- MTX
- AZA/6-MP
- Budesonide* (FDA Approved)
- Systemic Steroids
- Anti-TNF*
- Anti-Adhesion*
Moderate
- Budesonide*
- Antibiotics
- Aminosalicylates
- AZA/6-MP
- Budesonide*
- Systemic Steroids
- Anti-TNF*
- Anti-Adhesion*
Mild
- Budesonide*
- Aminosalicylates*

2-4 Years From Now:
Potential Therapeutic Pyramids
Crohn’s Disease | Ulcerative Colitis
--- | ---
Severe
- Surgery
- Anti-TNF*
- Anti-Adhesion
- MTX
- AZA/6-MP
- Budesonide* (FDA Approved)
- Systemic Steroids
- Anti-TNF*
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Moderate
- Anti-IL12/23
- Anti-Adhesion
- MTX
- AZA/6-MP
- Budesonide*
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- Anti-TNF*
Mild
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- Antibiotics
- Aminosalicylates
- AZA/6-MP
- Budesonide*
- Systemic Steroids
- Anti-TNF*

* FDA Approved

Antibiotics

Aminosalicylates

Anti-IL12/23

Anti-IL 6

Anti-Adhesion

Stem Cells
Russ’ Tip #1

• Use the Correct Mesalamine.

Optimizing Mesalamine

• Mild to moderate ulcerative colitis*
• Mild to moderate Crohn’s disease

Class: “Aminosalicylates”

Also called:
• 5-ASA
• Mesalazine
• Includes sulfasalazine (salazopyrin)

* FDA Approved
Optimizing Mesalamine

- Works topically
  - By contact with the mucosa of the bowel wall.
  - Not intended to be absorbed.
- Need to match the location of disease to the specific release mechanism of the various agents.
- Disclaimer: Brand names listed on next slide to avoid confusion.

Mesalamine Release Sites

- Pentasa®
- Asacol®
- Asacol-HD®
- Lialda®
- Azulfidine®
- Dipentum®
- Colazal®
- Glazo™

Stomach
Small Intestine
Large Intestine

Mechanisms of Release
- Moisture
- pH > 6; Moisture
- pH > 7; Moisture
- Azo-bond (orals)

Sources: FDA package inserts / company websites.
Mesalamine Release Sites

**Mechanisms of Release**
- **Moisture**: pH > 6; Moisture
- **Moisture pH > 7**: Moisture*
- **Azo-bond (orals)**: Directly applied (topicals)

Sources: FDA package inserts / company websites.

**Rowasa®**

Stomach
Small Intestine
Large Intestine

**Pentasa®, Apriso®, Asacol®, Asacol-HD®, Lialda®, Azulfidine®, Dipentum®, Colazal®, Giazo™, Canasa®**
Russ’ Tip #2

• Crohn’s Disease: Use Antibiotics in
  – Perianal disease
  – Penetrating disease
  – ? Stricturing

  May Need To
  Use Long-Term
  as in:
  Not Stop

• Ulcerative Colitis
  – Limited to “Pouchitis”

Rationale for Antibiotic Therapy in IBD

• ↓ Luminal bacterial concentrations
• Selectively eliminate bacterial subsets
• ↓ Tissue invasion, microabscesses
• ↓ Bacterial translocation, systemic dissemination
Russ’ Tip #3

A. Don’t Use Corticosteroids

B. You Will Need to Use Corticosteroids

C. When You Have a Patient on Corticosteroids, see “A” above.

Corticosteroid Therapies

- Oral, Parenteral, Topical (rectal)
- Effective in INDUCING REMISSION
- Ineffective in MAINTAINING REMISSION
- Prohibitive Side Effect Profile
Outcome of Steroid Therapy* for Patients With CD

1-Month Outcomes
- Remission: 48%
- Improved: 32%
- No response: 20%

1-Year Outcomes
- Remission: 54%
- Relapse: 46%
- Improved: 57%
- Relapse: 43%

Summary Outcomes
- Steroid Dependent: 36% (n=39)
- Prolonged Response: 44% (n=48)
- Steroid Resistant: 20% (n=22)

56%


Immediate and Prolonged Outcomes of Corticosteroid Therapy in UC

1-month Responses
- Complete: 54% (n=34)
- Partial: 30% (n=19)
- None: 16% (n=10)

1-year Responses
- Steroid Dependent: 22% (n=14)
- Prolonged Response: 49% (n=31)
- Surgery: 29% (n=18)

Budesonide

- High Potency
- Targeted Delivery To Bowel
- Extensive Hepatic First-Pass Metabolism
  - Fewer Steroid-Related Side Effects

“Customized” Budesonide For Crohn’s and now one also for Ulcerative Colitis

Budesonide: Customized for Crohn’s

Budesonide “Controlled Ileal Release (CIR)” (Entocort®-EC)

Enteric coating: Eudragit L (resistant up to pH 5.5)

Sugar core

Rate limiting polymer (ethyl cellulose) with budesonide

CIR pellet ~1 mm

Budesonide CIR: Absorption and Bioavailability

Systemic circulation
10%
Liver

60%-70% absorbed in the ileal and ileocecal area


BMD Loss Much Less with Budesonide CIR vs. Prednisolone

Budesonide CIR: Absorption and Bioavailability

Absorption and Bioavailability


Better Bone Mass Preservation vs Prednisolone in Corticosteroid-Naïve Crohn’s Disease Patients

Randomized, open-label, multicenter; n = 272 patients. Mean BMD change from baseline, expressed as T score ± SEM, during the 2-year study period in corticosteroid-naïve (N = 98) patients.

Oral Budesonide as Maintenance Treatment for Crohn’s Disease


Budesonide “Multi-Matrix Release (MMX)” (Uceris™)

- pH-resistant coating delays release until pH 7
- Hydrophilic excipient forms a viscous gel
- Lipophilic excipient prolongs dissolution

Budesonide: Customized for Ulcerative Colitis
Budesonide- MMX in UC: 8 Week Clinical Remission Rates

** USA Study **

- Placebo
- SASA 2.4g
- Bud-AMX 6mg
- Bud-AMX 9mg

** European Study **

- Placebo
- Bud-AMX 9mg
- Bud-AMX 18mg

* p<0.0143
** p<0.05; **p<0.025 vs. placebo

Russ’ Tip #4

- The Purine Analogues Are Reliable, Safe Long-Term Choices.
  - They are typically under-dosed.
  - They are should not be stopped if working.
  - You should use them more.

Purine Analogues

- 6-mercaptopurine
- Azathioprine

- Work SLOWLY….
- Wear off SLOWLY ….
- Be Patient …..
- Also should be used with anti-TNF’s as combined therapy ….

Efficacy of AZA as Crohn’s Disease Maintenance Therapy After Steroids in Adults*

* Remission induced by prednisolone tapered over 12 wk
Inclusion: Patients were not steroid dependent

Efficacy of 6-MP as Crohn’s Disease Maintenance Therapy After Steroids in Steroid-naïve Children

At baseline, patients received prednisone plus either 6-MP or placebo. Steroids were tapered after induction of remission.


6-MP Maintenance in UC

**Russ’ Tip #5**

Don’t Forget About Methotrexate!!
(Crohn’s Disease)

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**MTX in CD: Clinical Remission**

- **39%**
- **19%**

* Steroids discontinued or CDAI score ≤150 at 16 weeks
** P<0.025

MTX for Maintenance of Crohn’s

- Remission induced with MTX 25mg IM q week.
- Maintained with MTX 15mg IM q week vs. placebo.
- Week 40 Remission:
  - 65 % MTX
  - 39 % Placebo (p = 0.04)
- Prednisone for relapse:
  - 28% MTX
  - 58% Placebo (p = 0.01)


Maintenance of Improvement and Remission With MTX in CD

IM/SC 47%
Biologics

Biological Therapies

Anti-TNF:
- Infliximab (Remicade®)*
- Adalimumab (Humira®)*
- Certolizumab (Cimzia®)*

Golimumab (Simponi®)

* Currently FDA approved for IBD
Biological Therapies

Cellular Trafficking:
Natalizumab (Tysabri®)

Currently FDA approved for Crohn’s Disease

Russ’ Tip #7

• The biologics are “game changers” in IBD patients:
  – They work fast.
  – They work well.
  – They should be used repeatedly (ie. maintenance).
  – They should not be stopped if working.
  – We wait too long to start them.
  – We should use them more.
"Natural History" of Disease Behavior in CD

Impact of Therapy will Depend on Degree of Structural Damage & Velocity of Progression

Cosnes J et al. Inflamm Bowel Dis. 2002;8:244.
Maximizing Benefits with Biologics

1. Use Biologics Earlier
2. Give Induction “Load”
3. Continue Maintenance Therapy
4. Combine with an Immunosuppressive
   - azathioprine, 6-mercaptopurine, methotrexate

Early Intervention

• Response rates highest if start medications early in disease course.
  Crohn’s disease:
  – BEFORE stricturing / penetrating occurs
  Ulcerative colitis:
  – BEFORE chronic inflammation, “tubular colon”
• FDA indications are for moderate to severe disease.
Remission Rates Nearly Double With Early Use of Infliximab

Early Infliximab: Pediatric Moderate to Severe Crohn’s Disease*

![Graph showing remission rates with early use of Infliximab.](image)

*Median disease duration: 2 years. (REACH Trial).


Remission Rates Increase \(\approx 50\%\) With Early Use of Adalimumab

![Graph showing remission rates with early use of Adalimumab.](image)

*\(P=0.002\); **\(P<0.001\); †\(P=0.014\); ††\(P=0.001\); all vs placebo. (CHARM Trial).

Remission Rates Increase ≈ 50% With Early Use of Certolizumab

Clinical Response at Week 26

Clinical Remission at Week 26

*P<0.001; **P<0.01; †P<0.05; all vs placebo. (PRECiSE 2 Trial)


Step-Up vs Top-Down

Conventional Management vs Early Combined Immunosuppression

Step-Up (N=64)

Top-Down (N=65)

+ Infliximab

Infliximab (3 doses) + Azathioprine

Continue Azathioprine

+ Episodic Infliximab

Steroids

Top-Down Therapy in Crohn’s Disease: Results


Top-Down vs Step-Up

Endoscopic Results


*P=0.0028.
Maximizing Benefits

1. Use Biologics Earlier
2. Give Induction “Load”
3. Continue Maintenance Therapy
4. Combine with an Immunosuppressive
   - azathioprine, 6-mercaptopurine, methotrexate

Infliximab: Induction Dosing Increases Response Rate by 1/3

- Single Dose (n = 188)
- 3 Dose Induction (n = 385)
Adalimumab: Induction Dosing Doubles Remission Rate

<table>
<thead>
<tr>
<th>Dosing</th>
<th>Week 4 Remission</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=74)</td>
<td>12</td>
<td>0.36</td>
</tr>
<tr>
<td>40/20 mg (n=74)</td>
<td>18</td>
<td>0.06</td>
</tr>
<tr>
<td>80/40 mg (n=75)</td>
<td>24</td>
<td>0.001</td>
</tr>
<tr>
<td>160/80 mg (n=76)</td>
<td>36</td>
<td></td>
</tr>
</tbody>
</table>


Maximizing Benefits

1. Use Biologics Earlier
2. Give Induction “Load”
3. Continue Maintenance Therapy
4. Combine with an Immunosuppressive
   - azathioprine, 6-mercaptopurine, methotrexate
Don’t Stop

• Patient’s relapse off therapy
  – Clinical Trials
    • ACCENT I, II
    • ACT I, II
    • CLASSIC-2
    • CHARM
    • PRECISE 2
    • ENACT-2

Maximizing Benefits

1. Use Biologics Earlier
2. Give Induction “Load”
3. Continue Maintenance Therapy
4. Combine with an immunosuppressive
   • azathioprine, 6-mercaptopurine, methotrexate
Concomitant Immunomodulators

1. Decreased anti-drug antibodies
   - Some antibodies are neutralizing
   - Antibodies cause infusion reactions

Impact of Immunomodulators on Anti-Infliximab Antibodies

**ACCENT I**
Effect of Immunomodulators

- **Episodic**
  - No Immunomodulators: 38%
  - With Immunomodulators: 16%

- **Maintenance 5 mg/kg q8**
  - No Immunomodulators: 11%
  - With Immunomodulators: 7%

- **Maintenance 10 mg/kg q8**
  - No Immunomodulators: 8%
  - With Immunomodulators: 4%

Proportion of Patients

*ACCENT I: 442 patients with evaluable samples were assessed for ATI’s.*

Impact of Immunomodulators on Anti-Adalimumab Antibodies

- Rheumatoid Arthritis Study
  - Neutralizing in-vitro
  - Lower ACR-20 response
- CLASSIC II Study
  - 29% of antibody + in remission @ week 56


Certolizumab Immunogenicity

- Antibodies to certolizumab pegol – Crohn’s trials with continuous therapy

<table>
<thead>
<tr>
<th></th>
<th>PRECISE 1*</th>
<th>PRECISE 2†</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without IS†</td>
<td>10.2% (21/206)</td>
<td>12.5% (16/128)</td>
<td>11.1% (37/334)</td>
</tr>
<tr>
<td>With IS‡</td>
<td>4.0% (5/125)</td>
<td>2.3% (2/87)</td>
<td>3.3% (7/212)</td>
</tr>
</tbody>
</table>

*Certolizumab pegol administered at 400 mg every 4 weeks with an extra induction dose at week 2.
†IS = Immunosuppressants

4/16/2013
Concomitant Immunomodulators

1. Decreased anti-drug antibodies
   - Some antibodies are neutralizing
   - Antibodies cause infusion reactions
2. Does that translate into improved efficacy?
   - Initial clinical trials: no
   - Clinical experience: mixed
   - Recent randomized trials: Yes

Combination Therapy Increases Efficacy: Crohn’s Disease

SONIC Trial: Crohn’s Disease
Outcomes at Week 26

Steroid-free Remission

- Azathioprine: 30.6%
- Infliximab: 44.4%
- Combination: 56.8%

Mucosal Healing

- Azathioprine: 16.5%
- Infliximab: 30.1%
- Combination: 43.9%

P<0.001 vs. aza
P<0.001 vs. ifx
P=0.022 vs. ifx
P=0.055 vs. ifx

Combination Therapy Increases Efficacy: Ulcerative Colitis

UC-SUCCESS Trial: Ulcerative Colitis

Week 16 Corticosteroid-free Remission

- SONIC (Crohn’s)
  - 14% with infliximab alone
  - 1% if azathioprine + infliximab

- UC Success (UC)
  - 14% with infliximab alone
  - 1% if azathioprine + infliximab

Adding an immunomodulator greatly decreased antibodies to infliximab
Real World Translation:

• 1:7 patients will develop neutralizing antibodies if you use infliximab alone.

Vs.

• 1:100 patients will develop neutralizing antibodies if you use infliximab along with azathioprine.

Similar Rates Are Suspected For The Other Biologics

You Can Allow 1:7 Patient Develop Neutralizing Antibodies
Biologics in IBD

**The Promise**
- Fast Acting
- Efficacious
- Induction
- Maintenance
- Steroid Sparing
- Hospitalization Sparing
- Surgery Sparing

**The Threat**
- Infection Risk
- Neoplasm Risk
- Cost
- Running out of Options

or 1:100.
Biologics in IBD

The Promise
- Fast Acting
- Efficacious
- Induction
- Maintenance
- Steroid Sparing
- Hospitalization Sparing
- Surgery Sparing

The Threat
- Infection Risk
- Neoplasm Risk
- Cost
- Running out of Options

What is the Most Dangerous Medication Used in IBD?
### TREAT Registry: Serious Infections

Cox Regression Data (Multivariate)

<table>
<thead>
<tr>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current use of infliximab</td>
<td>1.402</td>
</tr>
<tr>
<td>Current use of 6MP/AZA/MTX</td>
<td>0.880</td>
</tr>
<tr>
<td>Current use of corticosteroids</td>
<td>2.014</td>
</tr>
<tr>
<td>Current use of narcotic analgesics</td>
<td>2.719</td>
</tr>
</tbody>
</table>

** p<0.0001


### TREAT Registry Update: Serious Infections

- **RR** = 1.45
- 95% CI = 1.10 – 1.91
- P = 0.0008

"Death" is not an Expected IBD Outcome

<table>
<thead>
<tr>
<th>Current use of infliximab</th>
<th>1.053</th>
<th>0.625-1.772</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current use of 6MP/AZA/MTX</td>
<td>0.760</td>
<td>0.465-1.241</td>
</tr>
<tr>
<td>Current use of corticosteroids</td>
<td>2.239</td>
<td>1.368-3.663 *</td>
</tr>
<tr>
<td>Current use of narcotic analgesics</td>
<td>2.629</td>
<td>1.601-4.317 **</td>
</tr>
</tbody>
</table>

* p<0.001, ** p<0.001

TREAT Registry Update: Mortality

RR = 0.91
95% CI = 0.68-1.21


“Yeah, but Don’t Them Medicines Cause Cancer ?”
TREAT Registry Update: Malignancies

Ré = 0.83
95% CI = 0.61-1.14

Ré = 0.80
95% CI = 0.31-2.07


Risk of NHL with anti-TNF + IM treatment for Crohn’s disease

Meta-analysis results
• 8905 patients representing 20,602 patient-years of exposure
• 13 NHL → 6.1 per 10,000 patient-years
• Mean age 52 years, 62% male
• 10/13 exposed to IM* (this is really a study of combination Rx)

<table>
<thead>
<tr>
<th>NHL rate per 10,000</th>
<th>SIR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEER database, all ages</td>
<td>1.9</td>
<td>–</td>
</tr>
<tr>
<td>IM alone</td>
<td>3.6</td>
<td>–</td>
</tr>
<tr>
<td>Anti-TNF + IM vs SEER</td>
<td>6.1</td>
<td>3.23</td>
</tr>
<tr>
<td>Anti-TNF + IM vs IM alone</td>
<td>6.1</td>
<td>1.7</td>
</tr>
</tbody>
</table>

*not reported in 2

IM: immunomodulator; SEER: Surveillance Epidemiology and End Results; SIR: standardised incidence ratio

Risk of developing lymphoma

Risk with azathioprine + anti-TNF

Hepatosplenic T-cell lymphoma
No Increase in Rate Reported

Anti-TNF + 6MP/AZA

- In 2006 → 130,000 IBD patients treated with infliximab
- In 2008 → 170,000 IBD patients treated with infliximab
- Over 1 million patients treated with anti-TNFs worldwide

6MP: 6 mercaptopurine; AZA: azathioprine

Centocor, data on file
PML Risk: Natalizumab

<table>
<thead>
<tr>
<th>Natalizumab Exposure</th>
<th>Anti-JCV Antibody + No Prior Immunodulators</th>
<th>Anti-JCV Antibody + Prior Immunodulators</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 – 24 months</td>
<td>&lt; 1 / 1,000</td>
<td>2 / 1000</td>
</tr>
<tr>
<td>25-48 months</td>
<td>5 / 1,000</td>
<td>11 / 1000</td>
</tr>
</tbody>
</table>

JC Virus: Free testing for antibody to JC virus; if negative, PML likely cannot occur

What About Cost?
Infliximab Use Shown to:

- Decrease Utilization of Hospitalizations and Surgeries
- Decrease Overall Costs
- Decrease Disability
- Increase Full-time Employment
- Increase Part-time Employment


Medical Cost-Utility: What is “Worth it?”

Colon CA Screen
HIV Therapy
HIDM
Hemodialysis
Fundoplication

Cost per Life Year Gained

$0
$25,000
$50,000
$75,000
$100,000

Pignone 2002; Freedberg 2001; CDC 2002;
Winkelmayer 2002; Heudebert 1997..
Medical Cost-Utility: What is “Worth it?”

Cost per Life Year Gained

$0 $25,000 $50,000 $75,000 $100,000

> $1 million

- Infliximab's
- Colon CA Screen
- HIV Therapy
- NIDDM
- Hemodialysis
- Fundoplication


And What About “Using Up Your Options?”

THE UNIVERSITY OF CHICAGO MEDICINE
IBD: Use Your Time Wisely

• Young Patients: Average age dx: 22!
• Chronic, Relapsing Disease
• Normal / Near Normal Life Expectancy

Maximize The Chances Your Biologic Will Work!
Maximize The Chances Your Biologic Will Last!

Previous and Current Therapeutic Paradigms

Previous
• Bottom-up approach
• Conservative use of immunomodulators
• Goals
  – Induce remission
  – Maintain remission
  – Prevent complications
  – Optimize surgical outcomes

Current
• Early aggressive approach
• Earlier use of immunomodulators
• Additional goals
  – Disease modification
  – Mucosal healing
  – Pharmacoconomics
• Disease prevention!
Key Points

• **5-ASA**
  – Know the location of the inflammation and the release.
  – Delivery mechanisms differ; may be relevant in some patients.

• **Corticosteroids**
  – Not for maintenance of remission.
  – Preferentially use budesonide if possible

• **Azathioprine/6MP**
  – Good long-term results. Maintain on therapy.

• **Biologics**
  – Extremely effective; Safer than alternatives.
  – Cost effective in many settings.

• **Future**
  – Agents already used in other diseases
  – Novel approaches