IBD
Understanding Your Medications

Thomas V. Aguirre, MD
Santa Barbara GI Consultants
IBD
Understanding Your Medications (& Your Doctor)
Thomas V. Aguirre, MD
Santa Barbara GI Consultants
Disclosure

• I do not work for any drug company
• I do not own any part of any drug company
• I do not receive any monetary or non-monetary benefit from any drug company
• I am not getting paid to be here today
IBD

- Ulcerative Colitis
  - continuous
  - colon only
  - mucosal
  - colectomy curative
  - hereditary less

- Crohns Disease
  - segmental
  - all gi tract
  - transmural
  - no cure
  - hereditary more
Armamentarium

- Aminosalicylates
  - Sulfasalazine
  - Mesalamine
- Steroids
  - Prednisone
  - Budesonide
  - Hydrocortisone (IV)
- Immunmodulators
  - Azathioprine= 6 mercaptopurine
- Biologics
  - Infliximab
  - Adalimumab
Armamentarium?

• Surgery*
• Diet
• Probiotics
• Antibiotics
• Stress management
• Biofeedback
• Herbs
• Acupuncture
Armamentarium

- Methotrexate
- Certolizumab pegol
- Natalizumab
When to Use What

- Evidence
- Anemia
- Weight loss
- Diarrhea
- Blood in stool
- Abdominal pain
- Extraintestinal manifestations
- Inflammatory blood tests
- Overall sense of well being
- Failure of first line medications
State of Illness

• Active
  – Remission (steroids)

• Quiescent
  – Maintenance

• Deep remission/maintenance
  – No evidence of inflammation on imaging or endoscopy
How They Work

• Topically
  – Aminosalicylates
  – Budesonide

• Systemically
  – Modify immune system
    • Azathioprine, steroids
  – Manipulation of innate immune systems
    • Biologics (infliximab)
Aminosalicylates

• First line
• Mild to moderate symptoms
• Works topically
• Crohn’s Disease
  – Benefit controversial in maintenance
  – May benefit in remission
• Ulcerative Colitis
  – Better than placebo
  – Topical
  – Oral
    • 4.8 grams
    • 3-6 weeks for maximal benefit

Am J Gastroenterol. 2011 Apr;106(4):617-29
Steroids

- **Prednisone**
  - 60 to 80% respond to 40-60mg dosage
  - No benefit to long term use
- **Budesonide**
  - Right sided CD
  - Less effective
  - Less side effects
  - No long term benefit
Immunomodulators

- Azathioprine/6-Mercaptopurine
- Induction of remission
- Maintenance of remission
- Steroid sparing agent
- Enzyme testing
- Routine blood test (blood count/liver test)
- May take 12 weeks for maximum benefit
Biologics

• Infliximab
• Infusion
• Remission
• Maintenance
• Sonic study
• Hepatosplenic T-cell lymphoma (HSTCL) combo therapy (1 in 45,000 young males)
Biologics

- Adalimumab
- At home injections
- Inducing remission
- Maintaining remission
- May help infliximab failures
- Safety similar to infliximab
Immunomodulation in UC

- Severe
  - Surgery
  - Cyclosporine
  - BIOLOGICS
  - AZA/6-MP

- Moderate
  - Systemic Corticosteroids

- Mild
  - Oral Steroids
  - Aminosalicylates
**Immunomodulation in Crohn’s Disease**

- **Aminosalicylates**
- **Non-systemic Steroids**
- **Systemic Corticosteroids**
- **Biologics**
- **Surgery**

The diagram shows the hierarchy of treatment options based on the severity of the disease:

- **Mild**
  - Aminosalicylates

- **Moderate**
  - Non-systemic Steroids
  - Biologics

- **Severe**
  - Systemic Corticosteroids
  - Biologics
  - Surgery

- Additional treatments include Biologics and AZA/6-MP/MTX.
Treat for How Long?
## Crohn’s Disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Prior to Stopping 6MP/AZA</th>
<th>6MP/AZA stop or compare to placebo</th>
<th>Relapse Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT1</td>
<td>51 pts AZA 2mg/kg &gt; 6 mos remission</td>
<td>1 Year 26 AZA v 25 Placebo</td>
<td>AZA 5% Placebo 41%</td>
</tr>
<tr>
<td>RCT2</td>
<td>63 pts steroid induced remission 1 Year</td>
<td>33 AZA 30 Placebo</td>
<td>AZA 58% Placebo 93%</td>
</tr>
<tr>
<td>Audit3</td>
<td>120 pts 6MP 50mg (25-150 mg) &gt; 6mos remission</td>
<td>5 Years 84 cont 6MP v 36 stop</td>
<td>6MP cont 61% 6MP stop 85%</td>
</tr>
<tr>
<td>RCT4</td>
<td>83 pts AZA 1.5-2.0mg/kg &gt; 3.5 yrs remission</td>
<td>1.5 Years 40 AZA v 43 Placebo</td>
<td>AZA 8% Placebo 21%</td>
</tr>
<tr>
<td>Open5</td>
<td>66 pts from #4</td>
<td>&gt; 5 Years 66 pts stopped AZA</td>
<td>63% relapsed by 5 years</td>
</tr>
</tbody>
</table>

## Stopping 6MP/AZA in Ulcerative Colitis

<table>
<thead>
<tr>
<th>Study</th>
<th>Prior to Stopping 6MP/AZA</th>
<th>6MP/AZA stop or compare to placebo</th>
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</tr>
</thead>
<tbody>
<tr>
<td>RCT1</td>
<td>79 pts AZA 100 mg (50-200) &gt; 6 mos remission</td>
<td>1 Year 33 AZA v 34 Placebo</td>
<td>AZA 31% Placebo 61%</td>
</tr>
<tr>
<td>Rtrspct2 Review</td>
<td>622 AZA/6MP UC + CD pts 222 pts in &gt;6mos remission</td>
<td>5 Years 79 CD and 143 UC</td>
<td>1 Year 37% 5 Years 75%</td>
</tr>
<tr>
<td>Rtrspct3 Review</td>
<td>61pts 6MP 50mg (25-150 mg) &gt; 3mos remission</td>
<td>1 Year 39 cont 6MP v 22 stop</td>
<td>6MP cont 43% 6MP stop 77%</td>
</tr>
<tr>
<td>Rtrspct4 Review</td>
<td>127 pts AZA 2.0 mg/kg &gt; 3 mos remission</td>
<td>1.5 years 40 AZA v 43 placebo</td>
<td>1 year 35% 5 years 65%</td>
</tr>
</tbody>
</table>
Conclusions from 6MP/AZA Withdrawal Studies in IBD

• Numbers to Remember
• Relapse is common after stopping
• AZA/6MP
  – 1 year relapse rates: 50% (35% to 93%)
  – 5 year relapse rates: 75% (63 to 85%)
• Conclusion: For IBD patients in remission on 6MP/AZA and tolerating the meds –
• CONTINUE treatment
### Stopping Infliximab in CD

<table>
<thead>
<tr>
<th>Study</th>
<th>Prior to Stopping INF</th>
<th>Yrs f/u off of INF IMM treatment</th>
<th>Relapse Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open Label1</td>
<td>115 pts INF + AZA &gt; 1 yr remission</td>
<td>1 Year AZA</td>
<td>40%</td>
</tr>
<tr>
<td>Prsptcv Cohort2</td>
<td>354 pts in Remission on INF 48 stopped INF</td>
<td>7 Years AZA 44% 6MP 4% MTX 19%</td>
<td>1 Year 50% 7 Years 65%</td>
</tr>
<tr>
<td>Obsrvtnl Cohort2</td>
<td>614 pts on INF 110 in remission &gt;6 mos stopped INF</td>
<td>75 AZA 17 MTX</td>
<td>Time to relapse 47.3 mos</td>
</tr>
<tr>
<td>Prsptcv Cohort4</td>
<td>24 pts RCT postop study 5 of 10 in endosc remission onINF at 1 yr stopped the INF</td>
<td>5 Years 4 on AZA 1 on 5ASA</td>
<td>100% 3 restart INF2 had surgery</td>
</tr>
</tbody>
</table>

1. Louis et al. Gastroenterology 2009;136:A146
Conclusions from Infliximab Withdrawal Studies in Crohn’s Disease

Numbers to Remember

• Relapse Rates after stopping INF
  – 1 year relapse rate: 50% (40% - 58%)
  – 5 year relapse rate: 75% (65 -100%)

• Conclusions: For CD patients in remission on Infliximab and tolerating treatment –
• CONTINUE treatment
What are the main side-effects of 6MP/Azathioprine?

<table>
<thead>
<tr>
<th>Event</th>
<th>Frequency Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stop therapy due to adverse event</td>
<td>11%</td>
</tr>
<tr>
<td>Allergic reactions</td>
<td>2%</td>
</tr>
<tr>
<td>Nausea</td>
<td>2%</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>2%</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>3%</td>
</tr>
<tr>
<td>Serious infections</td>
<td>5%</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>0.04% (4/10,000)</td>
</tr>
</tbody>
</table>

Siegel CA, et al. APT 2005 (weighted average); Siegel CA, et al. CGH 2009
Opportunistic Infections: Infliximab

- Herpes
- Listeriosis
- CMV
- Atypical Mycobacterium
- Salmonellosis
- PCP
- Other
Viral Exacerbations

- HBV/HCV
- Herpes
- HIV
- HPV
- Epstein -Barr

TREAT was primarily designed to assess long-term safety of infliximab in Crohn's.
## TREAT REGISTRY
Serious Infections Logistic Regression (Multivariate)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current use of infliximab</td>
<td>1.088</td>
<td>0.578–2.048</td>
</tr>
<tr>
<td>Current use of 6MP/AZA/MTX</td>
<td>0.821</td>
<td>0.451–1.495</td>
</tr>
<tr>
<td>Current use of corticosteroids</td>
<td>2.315</td>
<td>1.563–6.06*</td>
</tr>
<tr>
<td>Current use of narcotic analgesics</td>
<td>3.079</td>
<td>1.227–4.368*</td>
</tr>
</tbody>
</table>
HEPATOSPLENIC T-CELL LYMPHOMAS

Rare postmarketing cases of hepatosplenetic T-cell lymphoma have been reported in adolescent and young adult patients with Crohn’s disease treated with REMICADE. This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal. All of these hepatosplenetic T-cell lymphomas with REMICADE have occurred in patients on concomitant treatment with azathioprine or 6-mercaptopurine.

Revised September 2006
Hepatosplenic T cell Lymphoma

• Rare form of lymphoma
  – Approximately 5% of all T cell lymphomas
  – 100+ reports in the literature
    • Post-organ transplant
    • IBD (CD treated with AZA n=2)
  – AERS
    • 8 cases with infliximab
    • 2 azathioprine / 6MP alone
    • 0 adalimumab, etanercept

<table>
<thead>
<tr>
<th></th>
<th>Infliximab</th>
<th>Non-Infliximab</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Cancer</td>
<td>0.53</td>
<td>0.49</td>
<td>1.05</td>
<td>0.53-2.08</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>0.10</td>
<td>0.06</td>
<td>1.69</td>
<td>0.30-8.99</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Current use of infliximab</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current use of 6MP/AZA/MTX</td>
<td>0.731</td>
<td>0.398–1.340</td>
</tr>
<tr>
<td>Current use of corticosteroids</td>
<td>2.096</td>
<td>1.147–3.832*</td>
</tr>
<tr>
<td>Current use of narcotic analgesics</td>
<td>1.787</td>
<td>0.946–3.379</td>
</tr>
</tbody>
</table>
My Philosophy

• Patient Acceptance
  – Chronic disease
  – Complex illness
  – Psychiatric component (self image)

• Patient Understanding
  – Rarely absolutes
  – Internet hear say
  – Magic Bullet

• Patient Trust
  – Long term relationship
  – Open discussion
  – Mutual respect