Balancing the Risks and Benefits of Treatment for Inflammatory Bowel Diseases

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The Inflammatory Bowel Diseases (IBD) Medicine Cabinet

• 5-Aminosalicylates (5-ASAs)
  – Balsalazide (Colazal®), mesalamine (Asacol®, Lialda®, Pentasa®), sulfasalazine (Azulfidine®)
• Antibiotics
  – Ciprofloxacin (Cipro®), metronidazole (Flagyl®)
• Corticosteroids
  – Hydrocortisone, methylprednisolone (Solu-Medrol®), prednisone
  – Budesonide (Entocort®)
• Immunomodulators (IMs)
  – 6-Mercaptopurine (6MP), azathioprine (Azasan®, Imuran®)
  – Methotrexate
• Biologics
  – Adalimumab (Humira®), certolizumab pegol (Cimzia®), infliximab (Remicade®), natalizumab (Tysabri®)

Topics To Be Reviewed

• Benefits and risks of immunomodulators
• Benefits and risks of biologics
• Learning and making trade-offs
• Decoding the numbers game
Immunomodulators

• Also called “immune suppressants” or “antimetabolites”
• Search the Internet responsibly – they were used for years as “chemotherapy”
• Have been used since the 1970s for the treatment of IBD
• They work by quieting down the immune system

What is the Efficacy of 6-Mercaptopurine/Azathioprine (6MP/AZA)?

• These medications can take 2–4 months to fully “kick-in”
• Usually taken along with another medication to get patients into remission
• Once in remission, about 70% (70 out of 100) of patients stay in remission for at least one year

What Are the Main Side Effects of 6MP/AZA?

<table>
<thead>
<tr>
<th>Event</th>
<th>Estimated Frequency (annual)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic reactions</td>
<td>3% (3/100)</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>3% (3/100)</td>
</tr>
<tr>
<td>Serious infection</td>
<td>5% (5/100)</td>
</tr>
<tr>
<td>Death from serious infection (sepsis)</td>
<td>0.15% (15/10,000)</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma (NHL)</td>
<td>0.04% (4/10,000)</td>
</tr>
<tr>
<td>Death from lymphoma</td>
<td>0.01%–0.02% (1–2/10,000)</td>
</tr>
</tbody>
</table>


A Risk Palette

Read as: if 10,000 people were treated with drug X for 1 year, we would expect this many people to ________
Risk of Dying From a Serious Infection

Patient with Crohn’s disease receiving 6MP/AZA

Estimated annual risk = 15 per 10,000 treated patients


Annual Risk for Developing NHL in the US

0.02% = 2/10,000

Surveillance, Epidemiology, and End Results (SEER) Database, 2007.
Annual Risk for Developing NHL While On 6MP/AZA

0.04% = 4/10,000


Topics To Be Reviewed

• Benefits and risks of immunomodulators
• Benefits and risks of biologics
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**What Is Biologic Therapy?**

**Technical Answer**
- Biologic therapy is any therapy (medication) that is made from living organisms (humans, other animals, bacteria, plants)
  - The medication is similar or identical to the actual biologic chemicals that our body makes

**Practical answer for IBD**
- Designer drugs made to specifically **block** inflammation or **stimulate** anti-inflammatory processes

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**Smart Bomb**

While the other explosives played during recess, Charlie studied diligently in hopes of one day becoming a Smart Bomb.
IBD Biologic Treatment Made Simple

IFN=interferon; IL=interleukin; IL-1ra=interleukin 1 receptor antagonist; TGF=transforming growth factor; TNF=tumor necrosis factor.

The Antibodies (Medications) Block Chemicals That Cause Inflammation

Blocking chemicals decreases inflammation

Is There a Difference Between the Available Biologics?

- Infliximab, adalimumab and certolizumab pegol are all anti-TNF drugs
  - Infliximab → Intravenous every 8 weeks
  - Adalimumab → Subcutaneous injection every 2 weeks
  - Certolizumab → Subcutaneous injection every 4 weeks

- Natalizumab is an antiadhesion molecule
  - Recently approved by the US FDA
  - Natalizumab → Intravenous infusion every 4 weeks
  - TOUCH™ (Tysabri Outreach: Unified Commitment to Health) program

How Effective Is Treatment With Anti-TNF Therapy?
(Adalimumab, Certolizumab, Infliximab)

Within a few weeks of starting treatment with an anti-TNF drug:

- 40% (40/100) did not have an improvement in their symptoms
- 60% (60/100) had an improvement in their symptoms

Results based on a weighted average from PRECISE 2 (only response included since 6-month endpoint), ACCENT1, and CHARM studies.
How Effective Is Treatment With Anti-TNF Therapy?
(Adalimumab, Certolizumab, Infliximab)

Within a few weeks of starting treatment with an anti-TNF drug:

- 40% (40/100) did not have an improvement in their symptoms
- 60% (60/100) had an improvement in their symptoms

For those who improved, after 1 year of either continued treatment with the anti-TNF medication or with placebo, this is what happened:

<table>
<thead>
<tr>
<th></th>
<th>Anti-TNF</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>How many people were free from symptoms of Crohn’s disease?</td>
<td>34% (34 in 100)</td>
<td>13% (13 in 100)</td>
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</tbody>
</table>

Results based on a weighted average from PRECISE 2 (only response included since 6-month endpoint), ACCENT1, and CHARM studies.

Side Effects of Anti-TNF Agents

- Hypersensitivity reactions
  - Infusion or injection site reactions
  - Serum sickness/delayed hypersensitivity
- Immunogenicity
- Headache
- Rash
- Infections
  - *Mild and serious*
- Demyelinating disorders
- Autoantibodies
- Pancreatitis
- Heart failure
- Hepatotoxicity
- Malignancy
### The Main Side Effects of Anti-TNF Treatment

If 10,000 patients were treated for one year

<table>
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<tr>
<th>Event</th>
<th>Estimated Frequency</th>
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<tbody>
<tr>
<td>NHL (baseline)</td>
<td>2/10,000</td>
</tr>
<tr>
<td>NHL (on IMs)</td>
<td>4/10,000</td>
</tr>
<tr>
<td>NHL (on anti-TNF)</td>
<td>6/10,000</td>
</tr>
<tr>
<td>Hepatosplenic T-cell lymphoma</td>
<td>Unknown</td>
</tr>
<tr>
<td>Death from sepsis (lower for younger patients)</td>
<td>4/1000</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>5/10,000</td>
</tr>
</tbody>
</table>

Adapted from Siegel CA. In *Inflammatory Bowel Disease: Translating Basic Science Into Clinical Practice*. In press, 2008.

### Risk of Dying From a Serious Infection

Patient with Crohn's disease receiving combination anti-TNF + immunomodulators

Estimated annual risk = 40 per 10,000 treated patients

- Average age in 60s
- Risk highest if taking steroids or narcotics
- Risk highest with longer duration of disease and if other medical problems
- In younger patients, risk is much lower

Annual Risk for NHL While Taking an Anti-TNF + IM


What is Hepatosplenic T-cell Lymphoma?

- A type of NHL
- Symptoms and signs
  - Fevers, chills, night sweats that do not go away
  - Enlarged liver and spleen
  - Low blood counts
- Diagnosis made by biopsy of the liver, spleen or bone marrow
- Particularly nasty type of cancer that is difficult to treat
What Does Hepatosplenic T-cell Lymphoma Have To Do With IBD?

• Reported in patients taking azathioprine
  – 9 cases reported
• Reported in patients taking infliximab + azathioprine or 6MP
  – 16 cases reported
  – Young people (average age 23)
  – Most are male
• Out of a lot of patients
  – About 400,000 IBD patients treated with infliximab
  – Over 1 million patients treated with infliximab for all different uses worldwide

Natalizumab

• A new way of treating Crohn’s disease
• Also used to treat multiple sclerosis
• Only used for patients who have failed an anti-TNF agent
• Concern about a serious neurologic problem called progressive multifocal leukoencephalopathy (PML)
### Treatment With Natalizumab

**Patients who have failed anti-TNF therapy**

After 10 weeks of treatment with natalizumab

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<tr>
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<th>Natalizumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>How many patients had improvement of symptoms of Crohn’s disease?</td>
<td>51%</td>
<td>41%</td>
</tr>
<tr>
<td></td>
<td>51 in 100</td>
<td>41 in 100</td>
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Results based on data from ENACT 1 and 2.


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### Treatment With Natalizumab

**Patients who have failed anti-TNF therapy**

After 10 weeks of starting treatment with natalizumab

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Of those who improved, after 15 months of continued treatment with either natalizumab or placebo, this is what happened:

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<thead>
<tr>
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<th>Natalizumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>How many patients were free from symptoms of Crohn’s disease?</td>
<td>47%</td>
<td>18%</td>
</tr>
<tr>
<td></td>
<td>47 in 100</td>
<td>18 in 100</td>
</tr>
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</table>

Results based on data from ENACT 1 and 2.

Natalizumab

- Ten cases of JC virus–related PML in the world
  - Nine patients with multiple sclerosis (MS)
  - One patient with Crohn’s disease
- As of April 2009
  - > 52,000 patients have received natalizumab
  - > 6,800 patients have been treated for longer than 2 years
- What are the other options?
  - Surgery, clinical trials

Estimated Risk for Developing PML

If 10,000 patients were treated with natalizumab for 1 year

Estimated annual risk = 7 per 10,000 treated patients

- Average age 50
- Men and women
- Diagnosed from 8–37 infusions
- 9 patients with MS, 1 with Crohn’s
Treatment Pyramid for Crohn’s Disease

Natalizumab
Infliximab
Adalimumab
Certolizumab

AZA/6-MP
Methotrexate
Systemic steroids

Budesonide
Antibiotics
5-Aminosalicylates

Severe
Mod
Mild

Treatment Pyramid for Ulcerative Colitis

Surgery

Infliximab
Cyclosporine

6MP/AZA
Systemic steroids

5-Aminosalicylates

Surgery

Surgery

Surgery
Are Two Drugs Better Than One for Crohn’s disease?

- A recent research study was performed to test whether treatment was more effective with
  - Azathioprine alone
  - Infliximab alone
  - A combination of azathioprine and infliximab

After 6 Months of Treatment

<table>
<thead>
<tr>
<th></th>
<th>Azathioprine</th>
<th>Infliximab</th>
<th>Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>How many people were free from symptoms and off of prednisone?</td>
<td>31% (32 in 100)</td>
<td>44% (44 in 100)</td>
<td>57% (57 in 100)</td>
</tr>
<tr>
<td>How many had a completely normal colonoscopy after treatment?</td>
<td>17% (17 in 100)</td>
<td>30% (30 in 100)</td>
<td>44% (44 in 100)</td>
</tr>
<tr>
<td>Serious side effects</td>
<td>Equal across the groups</td>
<td></td>
<td></td>
</tr>
</tbody>
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But, some side effects may occur more often with 2 drugs. Which would you prefer?
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Risks Associated With IBD

- If IBD is not controlled it usually leads to surgery
  - Chance of requiring surgery for Crohn’s disease
    - Within 1 year of diagnosis: 40%
    - Within 5 years of diagnosis: 50%
    - Within 20 years of diagnosis: 80%
  - Chance of requiring surgery (colectomy) for ulcerative colitis
    - Within 20 years of diagnosis: 20%

Patients’ Willingness to Take Risk

MAR=maximum acceptable risk.

Putting Risk in Perspective

- Over a lifetime, the chance of dying from
  - Lightning: 1 out of 80,000
  - Bicycling accident: 1 out of 5,000
  - Drowning: 1 out of 1,000
  - Car accident: 1 out of 261
  - Cancer: 1 out of 8
  - Heart disease: 1 out of 5

Topics To Be Reviewed

• Benefits and risks of immunomodulators
• Benefits and risks of biologics
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This Is Doctor Talk

Not very useful to help make a decision about treatment

0.01%  RR = 1.48
SIR = 3.23
NNT = 7
OR = 14.5
P < 0.05
This Is Doctor Double-Talk

- “Framing” is the term used to present the same results in different ways\textsuperscript{1,2}
  - Relative risk = 34% reduction in heart attacks
  - Absolute risk = 1.4% reduction in heart attacks
  - Number needed to treat = 71

All show that treatment decreases chance of heart attack from 4.1% $\rightarrow$ 2.7%


Weighing the Risks Against the Benefits

It is an individual decision . . . but also keep in mind the risks of “under-treating” the disease

| SCARY but very rare side effects | EFFECTIVE drugs with the ability to induce remission . . . but not in everyone |

Risks of Treatment  

Benefits of Treatment
Summary

• Immunomodulator and biologic medications can dramatically improve the quality of life in IBD
• There are some very serious, but very rare side effects associated with these medications
• If you need the medication, the benefits most likely outweigh the risks
• Clearly understand the trade-offs so that you can make a decision that is right for you

Life Is Full of Risks, and Some Are Worth Taking

Thank You