Addressing Risks and Benefits In IBD

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• "Jaw Dropping Discovery Leads To 4 Simple Steps That Are Guaranteed To Permanently Eliminate And Prevent Painful Crohn's Disease Once And For All With No Side Effects or Risk - Or Your Money Back"

• Without Expensive Procedures
• Without Extreme Dietary Changes
• Without Steroid Dependencies
• Without Risk!

www.nomorecrohnsdisease.com
The Risk is Commensurate with the Reward

(Usually)
Disease Activity

“severe”

“moderate”

“mild”
Disease Activity

“severe”

“moderate”

“mild”

Degree of Risk

“high risk”

“low risk”
Biologic Agents (Remicade, Humira, Tysabri)

Severity of Disease

Degree of Risk

Cyclosporin, Clinical Trials, Surgery

“high risk”

“severe”

Oral steroids (Prednisone, Entocort)

Immunomodulators (6MP, Imuran, methotrexate)

“low risk”

“mild”

Antibiotics

Aminosalicylates

Non-systemic steroids
Balancing Treatment Benefit and Risk

- Improved quality of life
- Avoid Surgery
- Growth and Development
- Reduce cancer risk?

Benefits

- Known side effects
- Reactions
- Increased cancer risk?
- The Unknown

Risks
“There are **risks** and costs to a program of action. But they are far less than the **long-range risks** and costs of comfortable inaction.”

*John F. Kennedy*
Balancing Benefits and Risks of Treatment vs Benefits and Risks of No Treatment
Balancing Benefits and Risks of Treatment vs Benefits and Risks of No Treatment
So... what **are** the risks of untreated disease?

*i.e.* what is the *natural history* of IBD?
Long-term Evolution of Disease Behavior in CD

Cumulative Probability (%)

Inflammatory

Penetrating

Stricturing

Patients at risk:
N= 2002 552 229 95 37

Cumulative Probability of Surgical Intervention in Crohn’s Disease

- Need for Repeat Surgery
- Possible permanent stoma
- Malnutrition, Vitamin def
- Short bowel syndrome
- Operative risks

Natural History of Ulcerative Colitis

- Acute severe colitis: untreated mortality 24%
- Up to 30% undergo colectomy at some point
- Increased risk of colon cancer (probably related to degree/duration of longstanding inflammation)

Ekbom et al. NEJM 1990; 323 (18):1228-33
Rubin DT et al. Curr Treat Options Gastro 2006
What are the risks of “Conventional Therapy?”
## Steroids: Glass Half Empty or Half Full?

<table>
<thead>
<tr>
<th>Event</th>
<th>Estimated Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any side-effect leading to stopping prednisone</td>
<td>55%</td>
</tr>
<tr>
<td>Ankle swelling</td>
<td>11%</td>
</tr>
<tr>
<td>Facial swelling</td>
<td>35%</td>
</tr>
<tr>
<td>Easy bruising</td>
<td>7%</td>
</tr>
<tr>
<td>Acne</td>
<td>50%</td>
</tr>
<tr>
<td>Memory problems</td>
<td>7%</td>
</tr>
<tr>
<td>Psychosis - confusion/agitation</td>
<td>1%</td>
</tr>
<tr>
<td>Infections</td>
<td>13%</td>
</tr>
<tr>
<td>Cataracts</td>
<td>9%</td>
</tr>
<tr>
<td>Increased intraocular pressure</td>
<td>22%</td>
</tr>
<tr>
<td>High blood pressure</td>
<td>13%</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>33%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Chance increases 10x</td>
</tr>
</tbody>
</table>

What are the main side-effects of 6MP/Azathioprine?

<table>
<thead>
<tr>
<th>Event</th>
<th>Estimate Frequency (annual)</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/abnormal LFTs</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
Benefits of Biologics

- Decreased hospitalizations
- Decreased surgeries
- Improvement in HRQOL
- Improvement in work/productivity

So...

What *are* the risks associated with (biologic) therapy?
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
- Psoriasis
- Autoantibodies
- Pancytopenia
- Heart failure
- Hepatotoxicity
- Malignancy
Adverse Reactions Associated with anti-TNF Treatment

<table>
<thead>
<tr>
<th>Event</th>
<th>Estimated Frequency (annual)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stop therapy due to adverse event</td>
<td>10%</td>
</tr>
<tr>
<td>Infusion or injection site reactions</td>
<td>3%-20%</td>
</tr>
<tr>
<td>Drug related lupus-like reaction</td>
<td>1% (1/100)</td>
</tr>
<tr>
<td>Serious infections</td>
<td>3% (3/100)</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>0.05% (5/10,000)</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma (combo)</td>
<td>0.06% (6/10,000)</td>
</tr>
<tr>
<td>Multiple sclerosis, heart failure, serious liver injury</td>
<td>Case reports only</td>
</tr>
</tbody>
</table>

Hepatosplenic T-cell lymphoma

- 12 cases in IBD with 6MP/AZA alone
- 19 cases in IBD patients taking infliximab or adalimumab with 6MP/AZA
  - Age range 12-58 years old
  - Average age = 26 years old
  - Almost all are male (18/19)
  - Infusions ranged from 1-24
  - 9 patients had ≤ 3 infusions
  - Four received adalimumab (after infliximab)
  - 1 received natalizumab (after 2 anti-TNFs)
  - Appears to be universally fatal

Kotlyar 2011
How Much Risk are Crohn’s Patients Willing to Accept?

• Web-based survey of 580 patients with Crohn’s disease

• Conjoint trade-off analysis

• Evaluated patients’ willingness to accept the risk of treatment related side-effects in exchange for improvement in daily symptoms

Patients are Willing to Take High Risks

Maximal Acceptable Risk (Annual %)

N = 580

"Real" Risk of PML or lymphoma < 1 per 1000

### Risk of Developing NH Lymphoma

20 year old male receiving anti-TNF + Immunomodulator Therapy for 1 year

<table>
<thead>
<tr>
<th>Ten Thousand People</th>
<th>Risk without medication</th>
<th>Risk with IM monotherapy</th>
<th>Risk with combination therapy</th>
</tr>
</thead>
</table>

*The Palisade® of 10,000 People* • *Risk Communication Format © John Pelling 2001* • *See www.riskcomm.com* • *We can only show you estimates. It is impossible to be certain whether your results will be positive or negative.*
Summary: Risks & Benefits

- IBD itself carries significant risks if untreated.
- The risks of medical therapy are loosely correlated with respective benefits.
- Biologics can reduce hospitalizations, surgeries, and improve health-related quality of life.
- “Risks and Benefits” should be communicated effectively.
  - Relative to risk of untreated disease.
  - Using understandable means.
"We've considered every potential risk except the risks of avoiding all risks,"