Communicating with the IBD Patient: How to convey risks and benefits

October 30, 2011
ACG Postgraduate Course
National Harbor, Maryland

Corey A. Siegel, MD
Assistant Professor of Medicine
Dartmouth Medical School & The Dartmouth Institute for Health Policy and Clinical Practice
Director, Dartmouth-Hitchcock IBD Center

Risks of IBD Therapy

- Communicating data with patients
- Risks of immunomodulators
- Risks of biologics
- Are two drugs riskier than one?
- Risk compared to what?
Why are patients so afraid?

Risk Unknown
Not Observable
New Risk

• Nuclear accidents

Dread
Risk

• Biologics and NEW drugs

• Immunomodulators

Not Dreadful
Controllable
Equitable
Voluntary

• Steroids

Dreadful
Uncontrollable
Catastrophic
Involuntary

• 5-ASAs

Known Risks
Observable
Old Risk


How should we report data to patients?

SIR = 3.23
RR = 1.48
P < 0.05

OR = 14.5
NNT = 7

Common
Rare

0.01%
What do you mean when you say “rare” and “common”?
We asked patients what they think…

• “Rare”
  3 per million  → 20% (median 2%)
• “Common”
  5%  → 76% (median 30%)

Be careful with these words!

Numbers are hard!

• Numeracy (quantitative literacy)
  – ½ of patients were unable to convert:
    • 1% to 10 in 1000
  – 80% of patients were unable to convert:
    • 1 in 1000 to 0.1%
  – Patient have difficulty determining which is the higher risk:
    • 1 in 27 versus 1 in 37


Fair and Clear Communication of Risks and Benefits

• Beware of framing¹,²
  – Relative risk = 34% reduction in heart attacks
  – Absolute risk = 1.4% reduction in heart attacks

BOTH show that treatment decreases chance of Heart Attack from 4.1% \(\rightarrow\) 2.7%


Tips for Clear Communication

• Absolute risks better than relative risk
• Avoid decimals (0.06%)
• Keep common denominators (x/10,000)
• Visual aids help (turn numbers into pictures)
• Give perspective to other disease & life risks

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 AE</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%-0.09% (4-9/10,000)</td>
</tr>
</tbody>
</table>


Risk of Skin Cancer Associated with Thiopurines (CESAME)

- 19,486 IBD patients
- 32 cases of skin cancer (20 basal cell, 12 squamous)

Look at denominator

Wear sunscreen
Regular skin checks

Peyrin-Biroulet L, et al. ECCO 2011, abstract #15
### Adverse Events Associated with anti-TNF Treatment

<table>
<thead>
<tr>
<th>Event</th>
<th>Estimated Frequency</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%</td>
</tr>
<tr>
<td>Serious infections</td>
<td>3%</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>


### Risk of Dying from Sepsis on Infliximab: Systematic Review

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Design</th>
<th># Deaths from sepsis thought attributable to infliximab</th>
<th># of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ljung et al. Gut 2004</td>
<td>Population Based Cohort</td>
<td>1</td>
<td>191</td>
</tr>
<tr>
<td>Seiderer et al. Digestion 2004</td>
<td>Single-Center Cohort</td>
<td>0</td>
<td>92</td>
</tr>
<tr>
<td>Colombel et al. Gastroenterology 2004</td>
<td>Single-Center Cohort</td>
<td>5</td>
<td>500</td>
</tr>
<tr>
<td>Sands et al. NEJM 2004</td>
<td>Randomized Controlled Trial</td>
<td>2</td>
<td>282</td>
</tr>
<tr>
<td>Hanauer et al. Lancet 2002</td>
<td>Randomized Controlled Trial</td>
<td>1</td>
<td>573</td>
</tr>
<tr>
<td>Rutgeerts et al. Gastroenterology 1999</td>
<td>Randomized Controlled Trial</td>
<td>0</td>
<td>73</td>
</tr>
</tbody>
</table>

Risk of death from sepsis = 4/1000 pt-yrs

BUT it is a subgroup of patients at this high risk

- Older
  - Average age = 63 (systematic review); 67 (Mayo)
- Multiple co-morbidities
- Concomitant steroids and/or narcotics
- Longstanding disease

Young “healthy” patients are not in the clear, but probably much less at risk

Siegel, CGH 2006; Colombel, Gastro 2004
Lichtenstein CGH 2006
Toruner, Gastro 2008

Risk of Other Infections

- Invasive fungal infections
  - FDA warning 2008
  - Histoplasmosis, coccidiomycosis, blastomycosis
  - Unrecognized early disease
- Additional bacterial infections
  - FDA warning 2011
  - Listeria, Legionella
- Put these on your differential diagnosis
Risk of NH Lymphoma with anti-TNF + IM treatment for Crohn’s Disease
Meta-analysis Results

- 8905 patients representing 20,602 pt-years of exposure
- 13 Non-Hodgkin’s lymphomas → **6.1 per 10,000 pt-years**
- Mean age 52, 62% male
- 10/13 exposed to IM* (really a study of combo Rx)

<table>
<thead>
<tr>
<th></th>
<th>NHL rate per 10,000</th>
<th>SIR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEER all ages</td>
<td>1.9</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IM alone</td>
<td>3.6</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Anti-TNF + IM vs SEER</td>
<td>6.1</td>
<td>3.23</td>
<td>1.5-6.9</td>
</tr>
<tr>
<td>Anti-TNF+ IM vs IM alone</td>
<td>6.1</td>
<td>1.7</td>
<td>0.5-7.1</td>
</tr>
</tbody>
</table>

Siegel et al, CGH 2009:7:874. *not reported in 2

Risk of Developing non-Hodgkin’s Lymphoma
Patient receiving Immunomodulator +/- anti-TNF Therapy for 1 year

Risk of lymphoma with immune suppression
Solid Tumors and anti-TNF Treatment

- 13,000 patients enrolled, 49% received biologics

<table>
<thead>
<tr>
<th>Type of Cancer</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cancers</td>
<td>1.0 (0.8-1.2)</td>
</tr>
<tr>
<td>All solid tumors</td>
<td>1.0 (0.8-1.2)</td>
</tr>
<tr>
<td>Colon</td>
<td>0.8 (0.3-1.7)</td>
</tr>
<tr>
<td>Lung</td>
<td>1.1 (0.7-1.8)</td>
</tr>
<tr>
<td>Breast</td>
<td>0.9 (0.5-1.3)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>0.5 (0.1-2.6)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>2.3 (0.9-5.4)</td>
</tr>
<tr>
<td>Non-melanoma skin</td>
<td>1.5 (1.2-1.8)</td>
</tr>
</tbody>
</table>

Wolfe, Arthritis and Rheumatism 2007;56:2886.

Are two drugs riskier than one?

Anti-TNF monotherapy versus combination therapy with immunomodulators
Are serious infections more common if taking more than 1 medication?

- **TREAT registry**
  - Corticosteroids (HR 2.0, 95% CI 1.4-2.9)
  - Narcotics (HR 2.7, 95% CI 1.9-4.0)

- **Opportunistic infections**

<table>
<thead>
<tr>
<th>Prednisone, 6MP/AZA, Infliximab</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 medication</td>
<td>2.9 (1.5–5.3)</td>
</tr>
<tr>
<td>2 or 3 medications</td>
<td>14.5 (4.9–43)</td>
</tr>
</tbody>
</table>

Lichtenstein CGH 2006; Toruner Gastro 2008

Closer look at the Mayo experience with opportunistic infections

<table>
<thead>
<tr>
<th>Number of meds</th>
<th>Cases</th>
<th>Controls</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>38</td>
<td>129</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>1</td>
<td>38</td>
<td>59</td>
<td>2.9 (1.5-5.3)</td>
</tr>
<tr>
<td>2 or 3</td>
<td>24</td>
<td>12</td>
<td>14.5 (4.9-43)</td>
</tr>
</tbody>
</table>

**Specific combinations**

- Corticosteroids alone: 16 cases, 27 controls; OR 2.2 (1.0-4.9)
- 6MP/AZA alone: 20 cases, 31 controls; OR 3.4 (1.5-7.5)
- IFX alone: 3 cases, 2 controls; OR 11.1 (0.8-148)
- AZA/6MP + steroids: 16 cases, 6 controls; OR 17.5 (4.5-68)
- AZA/6MP + IFX: 1 case, 5 controls; OR 1.6 (0.1-19)
- AZA/6MP + IFX + steroids: 5 cases, 0 controls; OR 1.1 (1.0-1.2)

SONIC Safety Results

<table>
<thead>
<tr>
<th></th>
<th>AZA + placebo (n=161)</th>
<th>IFX + placebo (n=163)</th>
<th>IFX + AZA (n=179)</th>
<th>Total (n=503)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts with ≥ 1 AE, n (%)</td>
<td>138 (85.7%)</td>
<td>139 (85.3%)</td>
<td>156 (87.2%)</td>
<td>433 (86.1%)</td>
</tr>
<tr>
<td>Pts with ≥ 1 SAE, n (%)</td>
<td>39 (24.2%)</td>
<td>26 (16.0%)</td>
<td>25 (14.0%)</td>
<td>90 (17.9%)</td>
</tr>
<tr>
<td>Serious infections</td>
<td>8 (5.0%)</td>
<td>4 (2.5%)</td>
<td>6 (3.4%)</td>
<td>18 (3.6%)</td>
</tr>
</tbody>
</table>

Risk of infection same with 1 drug or 2 drugs


HSTCL – It’s not how many, it’s how often

- In 2006 → 130,000 IBD patients treated with infliximab
- In 2008 → 170,000 IBD patients treated with infliximab
- Over 400,000 IBD patients treated with infliximab worldwide

Centocor, data on file.
Natalizumab
Smarter use with the JC Virus Antibody Test

Anti-JCV Antibody Status

Negative

Positive (and prior IS use)

< 0.11/1000

0-2 years
1.2/1000

2+ years
8.1/1000
(1 in 125)

To ORDER anti-JC Virus antibody test:
Quest Labs test # 90257, JC Virus Antibody with Reflex Inhibition Assay
About 50% of Crohn’s patients will be positive

Compared to what?
What puts patients at the most risk… treatment or the disease (or life) itself?
Don’t forget about prednisone

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


Don’t forget about the high chance of requiring surgery for Crohn’s disease

As high as 50% within 5 years of diagnosis

Munkholm, Gastro 1993
Risk of Mortality in Crohn’s with Severe Disease & Steroids

- Retrospective cohort from UK (GPRD)
- 5,539 patients with Crohn’s; 41,624 controls
- Hazard Ratio for the risk of dying

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crohn’ s (mild)</td>
<td>1.27</td>
<td>1.07-1.51</td>
</tr>
<tr>
<td>Crohn’ s (severe)</td>
<td>2.44</td>
<td>1.84-3.25</td>
</tr>
<tr>
<td>Current prednisone</td>
<td>2.48</td>
<td>1.85-3.31</td>
</tr>
<tr>
<td>Current AZA/6MP</td>
<td>0.83</td>
<td>0.37-1.86</td>
</tr>
</tbody>
</table>

Lewis et al, AJG 2008; 103:1428.

Most patients are willing to take the risks of treatment

Summary: Risks of IBD Therapy

- IMs and biologics are associated with real, but small risks of serious adverse events
- Combination therapy does not appear to increase risk significantly
- Patients are willing to accept risk, as long as there is substantial benefit
- Clear communication to patients is critical

Life is full of risks, and many are worth taking