Communicating Risks and Benefits to IBD Patients

2008 Advances in Inflammatory Bowel Diseases
Crohn’s and Colitis Foundation’s Clinical and Research Conference

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How Can We Improve **Quality** of Care?

Institute of Medicine - *Crossing the Quality Chasm* (2001)

- S
- T
- E
- E
- P
How Can We Improve Quality of Care?
Institute of Medicine - *Crossing the Quality Chasm* (2001)

- **Safe**
  - Avoiding injuries to patients from the care that is intended to help them
- **Timely**
- **Effective**
- **Efficient**
- **Equitable**
- **Patient Centered**
  - Providing care that is respectful of and responsive to individual patient preferences, needs, and values, and ensuring that patient values guide all clinical decisions
Understanding and Clearly Communicating Risk & Benefit Information Will Lead to

- Safe
- Timely
- Effective
- Efficient
- Equitable Care for IBD
- Patient Centered and Improve Quality
Safety Update
Numbers We Can Tell Our Patients

• Risks of the disease
• Risks of the “old” drugs
• Risks of the “new drugs”
Risk of Mortality in Crohn’s with Steroids and Immunomodulators

- Retrospective cohort from UK (GPRD)
- 5,539 patients with Crohn’s; 41,624 controls
- Evaluated mortality associated with Crohn’s itself, prednisone, immunomodulators (most AZA & 6MP)
- Biologics not included in analysis

<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.
What is the risk of lymphoma associated with immunomodulators?

- Meta-analysis of 6 studies
- IBD patients treated with 6MP or Azathioprine have a 4-fold increased risk of developing lymphoma
- Subpopulation of Crohn’s & NHL (on IM)
  - 4 cases NHL/11,012 patient-years

3.6 NHLs per 10,000 patient-years

Excess risk of lymphoproliferative disorders in IBD: CESAME results

- 20,802 patients with 50,225 pt-yrs of follow up
- 29.8% patients on AZA, 3.5% MTX, 4.6% biologics
- 18 patients with NHL, 1 patient with Hodgkin lymphoma

13 of 19 taking AZA (1-16 yrs exposure)
Of 13 tested 9/13 EBV positive
9 patients younger than 60 years

Beaugerie L, et al. DDW 2008: #818

Interim Results... More to learn from this study!
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
- Pancytopenia
- Heart failure
- Hepatotoxicity
- Malignancy
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>Medications</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone, 6MP/AZA,</td>
<td></td>
</tr>
<tr>
<td>Infliximab</td>
<td>1 medication</td>
</tr>
<tr>
<td></td>
<td>2.9 (1.5–5.3)</td>
</tr>
<tr>
<td></td>
<td>2 or 3 medications</td>
</tr>
<tr>
<td></td>
<td>14.5 (4.9–43)</td>
</tr>
</tbody>
</table>

Lichtenstein CGH 2006; Toruner, Gastro 2008
### Risks of Dying from Sepsis on Infliximab

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Design</th>
<th># Deaths from sepsis in patients taking 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

Who are the patients who are dying from sepsis related to anti-TNF?

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

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

Siegel, CGH 2006; Colombel, Gastro 2004; Lichtenstein CGH 2006
Risk of NH Lymphoma with anti-TNF treatment for Crohn’s Disease

Meta-analysis Results

- 8905 patients representing 20,602 pt-years of exposure
- 13 Non-Hodgkin lymphomas → **6.1 per 10,000 pt-years**
- Mean age 52, 62% male
- 10/13 exposed to IM* (so this is 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 vs SEER</td>
<td>6.1</td>
<td>3.23</td>
<td>1.5-6.9</td>
</tr>
<tr>
<td>Anti-TNF vs IM alone</td>
<td>6.1</td>
<td>1.7</td>
<td>0.5-7.1</td>
</tr>
</tbody>
</table>

*Siegel et al, Gastro 2008;134(4):A14

*not reported in 2
Hepatosplenic T-cell lymphoma

• 9 cases in IBD with 6MP/AZA alone
• 16 cases in IBD patients taking infliximab or adalimumab with 6MP/AZA
  – Age range 12-58 years old
  – Average age = 23 years old
  – Almost all are male (15/16)
  – Infusions ranged from 1-24
  – 7 patients had ≤ 3 infusions
  – Three received adalimumab (after infliximab)
  – Appears to be universally fatal

Centocor, data on file.
HSTCL – How big of a problem is this?

- Over 1 Million anti-TNF treated patients worldwide
- About 4.5 Million patient-years of exposure
- No anti-TNF monotherapy (but not many out there)

Centocor, data on file.
HSTCL – How big of a problem is this?

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

Centocor, data on file.
Natalizumab

• SIX cases of JC virus related progressive multifocal leukoencephalopathy
  – Five patients with multiple sclerosis
  – One patient with Crohn’s disease
• As of late 2008
  – > 48,000 pts have received natalizumab
  – > 18,000 pts have been treated for longer than 1 year
• What is the tradeoff?
  – Response at week 4 → \( \text{NNT} = 7 \)
  – Maintenance of remission at week 36 → \( \text{NNT} = 6 \)
  – 1 patient with PML over 1 year → \( \text{NNH} \approx 3000 \)

Patient Centered
How should we tell patients?

If patients don’t understand the treatment options, they cannot make informed medical decisions

Clear communication of risks and benefits (by us – not by Google)
How to Communicate All of This to Patients?

- 0.01%
- \( SIR = 3.23 \)
- \( NNT = 103 \)
- \( RR = 1.48 \)
- \( P < 0.05 \)
- \( OR = 14.5 \)

Common
Rare
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
  - Data interpretation test → 20%-87% correct

How well do our patients understand statistics?

- 18 item test of medical data interpretation skills
- Wide-range of education level of the 178 participants
- Correct responses ranged from 20%-87%

Schwartz et al. Med Decis Making 2005
Tips for Clear Communication

• Less is more
• Absolute risks better than relative risk
• Avoid decimals (0.06%)
• Keep common denominators (x/1000)
• Visual aids help (turn numbers into pictures)
• Give perspective to other life risks
• Individualized estimates are best

Examples

-Numbers You Can Use -
## Absolute Rates Are Best

<table>
<thead>
<tr>
<th>Event</th>
<th>Estimated Frequency (annual, pt-years)</th>
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<tbody>
<tr>
<td>Non-Hodgkin Lymphoma (baseline)</td>
<td>2/10,000</td>
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<tr>
<td>Non-Hodgkin Lymphoma (on IM)</td>
<td>4/10,000</td>
</tr>
<tr>
<td>Non-Hodgkin Lymphoma (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</td>
<td>4/1000</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>5/10,000</td>
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SONIC Made Patient Friendly

508 patients were treated with either azathioprine, Remicade, or a combination of both medications. At the end of 6 months, this is what happened:

<table>
<thead>
<tr>
<th></th>
<th>Azathioprine</th>
<th>Remicade</th>
<th>Combination</th>
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<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>
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Sandborn, ACG 2008
How often do the anti-TNF drugs improve symptoms of Crohn’s disease? → NON-SMOKERS

<table>
<thead>
<tr>
<th></th>
<th>75%</th>
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Parsi et al. Gastro 2002
How often do the anti-TNF drugs improve symptoms of Crohn’s disease? → SMOKERS

Parsi et al. Gastro 2002
**Risk of Developing NH Lymphoma**

20 year old male receiving anti-TNF + Immunomodulator Therapy

| Risk with combination therapy |
|-----------------------------|---|
| 20 year old male receiving anti-TNF + Immunomodulator Therapy | |

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The Pechkin/Pechkin of 10,000 People Risk Communication Framers © John Pechkin 2001 See www.ribocm.com We can only show you estimates. It is impossible to be certain whether your results will be positive or negative.
Risk of Developing PML

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

Estimated annual risk = 3 per 10,000 treated patients
Life is Risky – Putting Risk in Perspective

Annual Risk

- Dying from lightning strike
- Dying in a motor-vehicle accident
A Prediction Model to Communicate Individualized Risk and Benefit Information

• Start with a well defined data set
• Cox proportional analyses to develop best predictive model
• System Dynamics Analysis (SDA) to graphically display results
• Take individual patient characteristics to show patients the predicted risk of their disease and benefit of treatment

Siegel, Siegel, Dubinsky, Sands, Kugathasan, Hyams, Markowitz, et al.
“High Risk Patient” – 16 year old girl with diffuse Crohn’s disease, 4th serologic quartile

Cumulative Probability of a Complication

- No treatment
- Early biologic treatment

Year from Present

0 1 2 3 4 5

percent

0 25 50 75 100
Model Control Panel and Output

“Low Risk Patient” – 8 year old girl with colonic Crohn’s disease, 2nd serologic quartile

Cumulative Probability of a Complication

No treatment

Early biologic treatment
Conclusion

• The exact amount of risk of biologic therapy is uncertain, but in absolute terms, it is very small
• Don’t let patients be scared by the wrong information (help them get it right – then they can decide)
• Tools are being developed to help us to better communicate with our patients
• By improving communication, we will be improving the quality of our care in IBD