What is risk anyway?

Risk = probability × consequence

But how people perceive risk may be the most important
Factors controlling risk perception

Known Risks
Observable
Old Risk

Risk Unknown
Not Observable
New Risk

Not Dreadful
Controllable
Equitable
Voluntary

Dread
Uncontrollable
Catastrophic
Involuntary

Nuclear accidents

• Nuclear accidents
• Railroad collisions

• Aspirin
• Downhill skiing

Voluntary
Equitable
Controllable
Not Dreadful


is not helping us
Numbers are hard!

- Numeracy (quantitative literacy)\(^1\)
  - \(\frac{1}{2}\) 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

Misleading patients is easy

- Beware of framing\(^1,2\)
  - 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%**

Medical literature is confusing

Tips for Clear Communication

- Less is more
- 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 life risks
- Individualized estimates are best
What are the main side-effects of 6MP/Azathioprine?

If 10,000 patients were treated for 1 year

<table>
<thead>
<tr>
<th>Event</th>
<th>Estimated Frequency (annual)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Having an Allergic reactions</td>
<td>3% (3/100)</td>
</tr>
<tr>
<td>Getting Pancreatitis</td>
<td>3% (3/100)</td>
</tr>
<tr>
<td>Getting a Serious Infection</td>
<td>5% (5/100)</td>
</tr>
<tr>
<td>Getting Non-Hodgkin’s Lymphoma</td>
<td>0.04% (4/10,000)</td>
</tr>
<tr>
<td>Dying from Lymphoma</td>
<td>0.01%-0.02% (1-2/10,000)</td>
</tr>
</tbody>
</table>


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</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea, headache</td>
<td>About the same as placebo</td>
</tr>
<tr>
<td>Infusion or injection site reactions</td>
<td>3%-20%</td>
</tr>
<tr>
<td>Delayed hypersensitivity reactions</td>
<td>1%</td>
</tr>
<tr>
<td>Drug related lupus</td>
<td>1%</td>
</tr>
<tr>
<td>Multiple sclerosis, heart failure, serious hepatic toxicity</td>
<td>Case Reports</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 – these aren’t YOUR patients

- Older
  - Average age = 63 (systematic review); 67 (Mayo)
  - OR 3.0 (95%CI 1.2-7.2) for > 50 yrs versus ≤ 24
- Multiple co-morbidities
- Concomitant steroids and/or narcotics
- Long-standing disease

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

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

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 lymphomas \( \rightarrow \) 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 + 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 NH Lymphoma

### Patient receiving anti-TNF + Immunomodulator Therapy for 1 year

<table>
<thead>
<tr>
<th>Ten Thousand People</th>
<th>Risk with combination therapy</th>
</tr>
</thead>
</table>

**One drug or two?**

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>1 medication</th>
<th>2 or 3 medications</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio (95% CI)</td>
<td>Odds Ratio (95% CI)</td>
</tr>
<tr>
<td></td>
<td>2.9 (1.5–5.3)</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><strong>2 or 3</strong></td>
<td><strong>24</strong>*</td>
<td><strong>12</strong></td>
<td><strong>14.5 (4.9-43)</strong></td>
</tr>
</tbody>
</table>

**Specific combinations**

<table>
<thead>
<tr>
<th>Corticosteroids alone</th>
<th>16</th>
<th>27</th>
<th>2.2 (1.0-4.9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6MP/AZA alone</td>
<td>20</td>
<td>31</td>
<td>3.4 (1.5-7.5)</td>
</tr>
<tr>
<td>IFX alone</td>
<td>3</td>
<td>2</td>
<td>11.1 (0.8-148)</td>
</tr>
<tr>
<td>AZA/6MP + steroids</td>
<td>16</td>
<td>6</td>
<td>17.5 (4.5-68)</td>
</tr>
<tr>
<td>AZA/6MP + IFX</td>
<td>1</td>
<td>5</td>
<td>1.6 (0.1-19)</td>
</tr>
<tr>
<td>AZA/6MP + IFX + steroids*</td>
<td>5</td>
<td>0</td>
<td>1.1 (1.0-1.2)</td>
</tr>
</tbody>
</table>

Toruner et al. Gastro 2008;134:929
Hepatosplenic T-cell lymphoma

- 9+ cases in IBD with 6MP/AZA alone
- 18 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 (17/18)
  - Infusions ranged from 1-24
  - 8 patients had ≤ 3 infusions
  - Three received adalimumab (after infliximab)
  - Appears to be universally fatal

Centocor, data on file.

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 1 million patients treated with anti-TNFs worldwide

Centocor, data on file.
Decision analysis to help guide us for using mono or combo therapy

- Decision analytic model
  - Decision tree model
    - IFX monotherapy vs IFX plus AZA combination therapy
    - Patient with moderate-severely active Crohn’s disease who is naïve to both anti-TNFs and immunomodulators
    - Time horizon one year

Sensitivity analyses to determine thresholds where overall benefit switches from combo → mono


The model shows us that combination therapy is favored unless...

<table>
<thead>
<tr>
<th></th>
<th>Base Case Estimate</th>
<th>Threshold at which monotherapy is favored</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission combo</td>
<td>46%</td>
<td>32%</td>
</tr>
<tr>
<td>Remission mono</td>
<td>35%</td>
<td>51%</td>
</tr>
<tr>
<td>SAE combo</td>
<td>11%</td>
<td>35%</td>
</tr>
<tr>
<td>Serious infection combo</td>
<td>4%</td>
<td>16%</td>
</tr>
<tr>
<td>Death from infection combo</td>
<td>11%</td>
<td>71%</td>
</tr>
<tr>
<td>Lymphoma combo</td>
<td>0.06%</td>
<td>4%</td>
</tr>
</tbody>
</table>

Monotherapy only favored when risks of combo become clinically unrealistic

Patients are Willing to Take High Risks

- PML
- Serious infection
- Lymphoma

N = 580

Risk of dying from PML or lymphoma < 1 per 1000

Parents are willing to take even higher risks of lymphoma… but only if their kids are sick!


HOW CAN THIS BE MADE EASIER FOR YOU, PATIENTS AND PARENTS?

System Dynamics Modeling to Predict and Display Individual Crohn’s Disease Patient Outcomes

Complex Clinical Data → Patient Friendly Results

Patient Population for Model Development

- 796 well characterized pediatric CD patients
- Enrolled from 21 centers from North America
- Demographic, clinical, genetic and immune response data were prospectively collected
- Treatment data collected
  - Steroids, Immunomodulators (IM), anti-TNF agents
  - Timing in relationship to a disease complication
- Model concordance index (Harrell’s C = 0.81)

Control Panel and Output

16 year old girl, small bowel and perianal disease, QSS group = 4

Risk of Complication

Overall RR: 1.2576
Benefit of therapy: 0.72

Treatment Options

1. Corticosteroids
2. Early Biologic Treatment

Corticosteroids

Early Biologic Treatment
**Summary: Risks & Benefits**

- Clear communication of risk is hard
- Keep things simple and be aware of how easy it is to frame data
- Combination therapy probably adds benefit, at a very small increase in absolute risk
- Patients & parents are willing to accept risk, as long as there is measurable benefit
- Prediction & communication tools will hopefully make this easier for all of us
Life is full of risks, and many are worth taking