IBD CME TV

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

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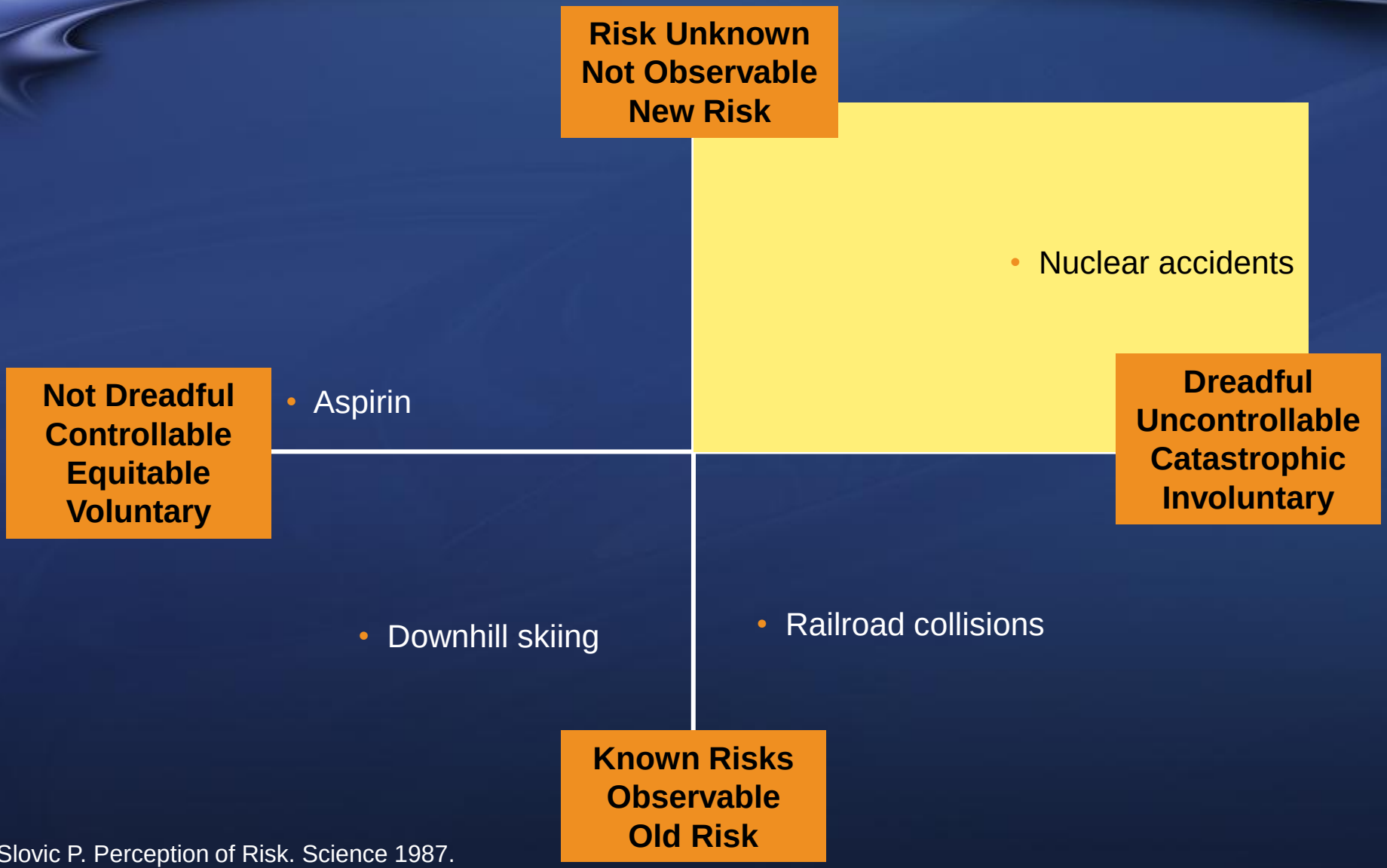
# Risks of IBD Therapy

- 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?




Slovic P. Perception of Risk. Science 1987.

# How should we report data to patients?

0.01%

RR = 1.48

SIR = 3.23

NNT = 7

P<0.05

Common

OR =14.5

Rare

# What do you mean by "rare" and "common"?

- "Rare"

  3 per million → 20% (median 2%)

- "Common"

  5% → 76% (median 30%)

- 63% of patients wanted to hear about <u>all</u> less-serious and life-threatening side-effects, even if the chance was less than 1 per 10,000

Siegel CA, et al. *Presented at DDW* 2011, Chicago, IL.

# 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

Schwartz LM et al. *Ann Intern Med.* 1997;127(11):966-72.
Sheridan SL, *Pignone M. Eff Clin Pract*. 2002;5:35.

# Fair and Clear Communication of Risks and Benefits

- Beware of framing[1,2]
  - Relative risk = 34% reduction in heart attacks
  - Absolute risk = 1.4% reduction in heart attacks


1. Malenka DJ et al. *J Gen Intern Med.* 1993;8:543-8.
2. Hux JE, *Naylor CD. Med Decis Making*. 1995;5:152-7.

# 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

Fagerlin et al. *Am J Health Behav* 2007. Peters et al. *Health Affairs* 2007.

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

| Event | Frequency Estimate |
|---|---|
| Stop therapy due to AE | 11% |
| Allergic reactions | 2% |
| Nausea | 2% |
| Hepatitis | 2% |
| Pancreatitis | 3% |
| Serious infections | 5% |
| non-Hodgkin's lymphoma | 0.04%-0.09% (4-9/10,000) |

Siegel CA, et al. *APT* 2005 (weighted average); Siegel CA, et al. *CGH* 2009; Beaugerie L, et al. *Lancet* 2009.

# Solid Tumors and Thiopurines

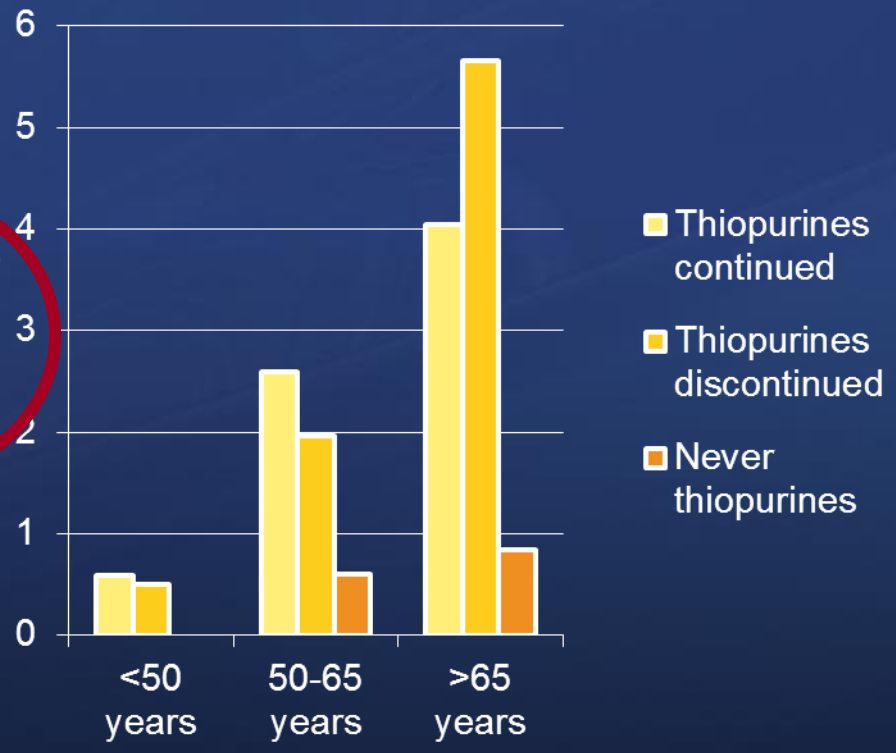
- UK study 1994 (Connell, Lancet)
  - 755 azathioprine treated IBD patients
  - No increased risk of solid tumors except slight increase in cervical cancer
- UK study 2002 (Fraser, APT)
  - Retrospective study including 2204 patients with IBD; 626 exposed to azathioprine
  - 4.5% of patients developed cancer in **BOTH groups**
  - No increase in colorectal, bronchial or breast CA

# 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

**Incidence rate per 1000 pt-years**




**Wear sunscreen**
**Regular skin checks**

Fagerlin et al. *Am J Health Behav* 2007. Peters et al. *Health Affairs* 2007.

# Adverse Events Associated with anti-TNF Treatment

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

Siegel CA. The risks of biologic therapy for inflammatory bowel disease. In Bernstein, ed. The inflammatory bowel disease yearbook, volume 6. In press; Infliximab package insert; Vermeire Gastro 2003; Cush, *Ann Rheum Dis* 2005; Lenercept study group, *Neurology* 1999; ATTACH trial 2003

# Risk of Dying from Sepsis on Infliximab: Systematic Review

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

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

Siegel et al. *Clin Gastroenterol Hepatol*. 2006;4:1017-1024.

# 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
- 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; 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

# 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)

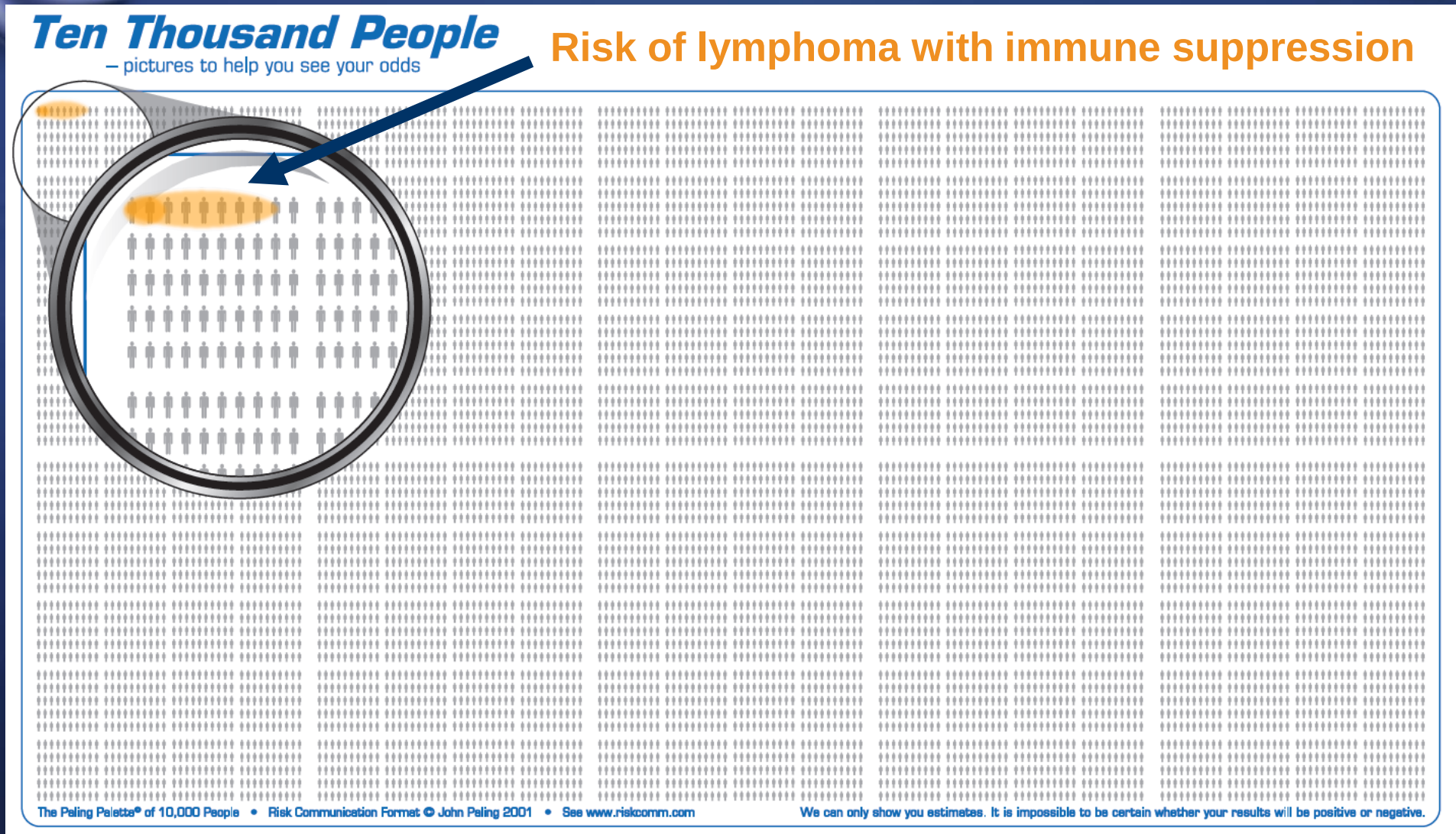
| | NHL rate per 10,000 | SIR | 95% CI |
|---|---|---|---|
| SEER all ages | 1.9 | - | - |
| IM alone | 3.6 | - | - |
| Anti-TNF + IM *vs* SEER | 6.1 | 3.23 | 1.5-6.9 |
| Anti-TNF+ IM *vs* IM alone | 6.1 | 1.7 | 0.5-7.1 |

*not reported in 2

Siegel et al, *CGH* 2009;7:874.

# Risk of Developing non-Hodgkin's Lymphoma

**Patient receiving Immunomodulator +/- anti-TNF Therapy for 1 year**



# Solid Tumors and anti-TNF Treatment

- National Data Bank for Rheumatic Diseases (1998-2005)
- 13,000 patients enrolled, 49% received biologics

| Type of Cancer | Odds Ratio |
|---|---|
| **All cancers** | **1.0 (0.8-1.2)** |
| All solid tumors | 1.0 (0.8-1.2) |
| Colon | 0.8 (0.3-1.7) |
| Lung | 1.1 (0.7-1.8) |
| Breast | 0.9 (0.5-1.3) |
| Pancreas | 0.5 (0.1-2.6) |
| Melanoma | 2.3 (0.9-5.4) |
| **Non-melanoma skin** | **1.5 (1.2-1.8)** |

Wolfe, *Arthritis and Rheumatism* 2007;56:2886.

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# 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

| Prednisone, 6MP/AZA, Infliximab | Odds Ratio (95% CI) |
|---|---|
| **1 medication** | 2.9 (1.5–5.3) |
| **2 or 3 medications** | 14.5 (4.9–43) |

Lichtenstein *CGH* 2006; Toruner, *Gastro* 2008

# Closer look at the Mayo experience with opportunistic infections

| Number of meds | Cases | Controls | OR |
|---|---|---|---|
| 0 | 38 | 129 | 1.0 (ref) |
| 1 | 38 | 59 | 2.9 (1.5-5.3) |
| **2 or 3** | **24** | **12** | **14.5 (4.9-43)** |

| Specific combinations | | | |
|---|---|---|---|
| Corticosteroids alone | 16 | 27 | 2.2 (1.0-4.9) |
| 6MP/AZA alone | 20 | 31 | 3.4 (1.5-7.5) |
| IFX alone | 3 | 2 | 11.1 (0.8-148) |
| **AZA/6MP + steroids** | **16** | **6** | **17.5 (4.5-68)** |
| **AZA/6MP + IFX** | **1** | **5** | **1.6 (0.1-19)** |
| AZA/6MP + IFX + steroids | 5 | 0 | 1.1 (1.0-1.2) |

Toruner et al. *Gastro* 2008;134:929

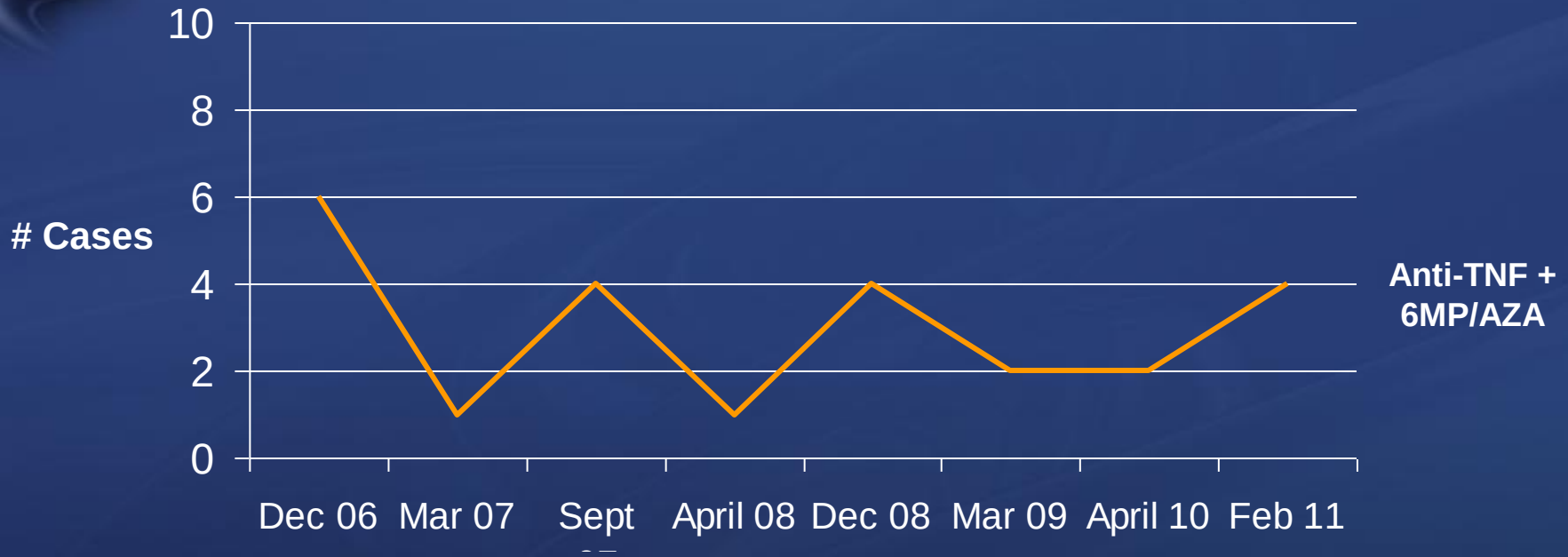
# SONIC Safety Results

| | AZA + placebo (n=161) | IFX + placebo (n=163) | IFX + AZA (n=179) | Total (n=503) |
|---|---|---|---|---|
| Pts with ≥ 1 AE, n (%) | 138 (85.7%) | 139 (85.3%) | 156 (87.2%) | 433 (86.1%) |
| Pts with ≥ 1 SAE, n (%) | 39 (24.2%) | 26 (16.0%) | 25 (14.0%) | 90 (17.9%) |
| **Serious infections** | **8 (5.0%)** | **4 (2.5%)** | **6 (3.4%)** | **18 (3.6%)** |

**Risk of infection same with 1 drug or 2 drugs**

Sandborn, WJ et al. *NEJM* 2010.

# HSTCL – It's not how many, it's how often

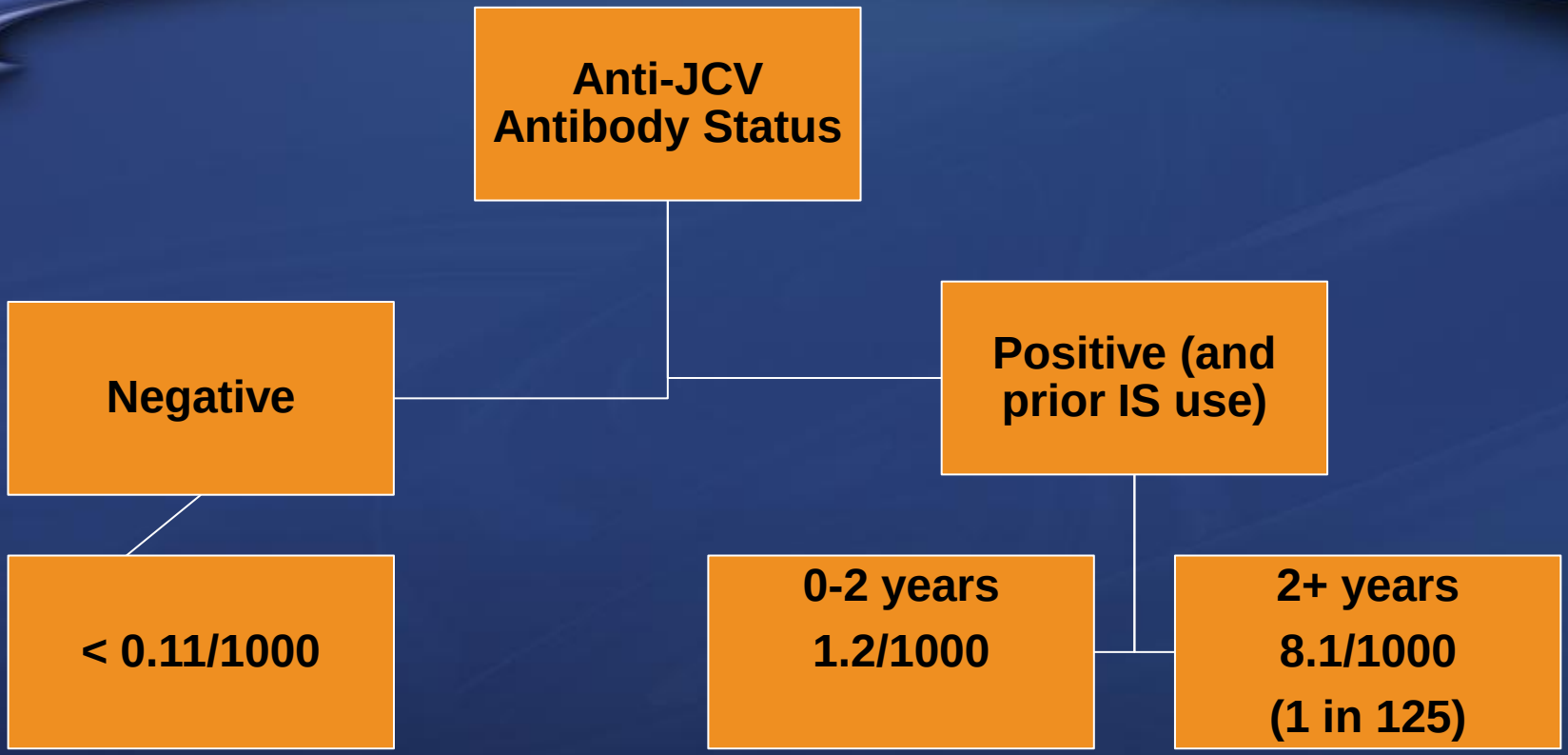



- In 2006 → 130,000 IBD patients treated with infliximab
- In 2008 → 170,000 IBD patients treated with infliximab
- Over 400,000 IBD patients treated with infliximab worldwide

Centocor, data on file.

# Natalizumab

## Smarter use with the JC Virus Antibody Test




**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**

Pepio et al. *DDW* 2011; Abstract # 1211

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# 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 |

Present IBD 2001, *Rutgeerts* APT 2001, *Rutgeerts* NEJM 1994

# 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

| Exposure | Hazard Ratio | 95% CI |
|---|---|---|
| Crohn's (mild) | 1.27 | 1.07-1.51 |
| **Crohn's (severe)** | **2.44** | **1.84-3.25** |
| **Current prednisone** | **2.48** | **1.85-3.31** |
| Current AZA/6MP | 0.83 | 0.37-1.86 |

Lewis et al, *AJG* 2008;103:1428.

# Putting Risk in Perspective

**Over a lifetime, the chance of dying from:**

Lightning →

Bicycling accident →

Drowning →

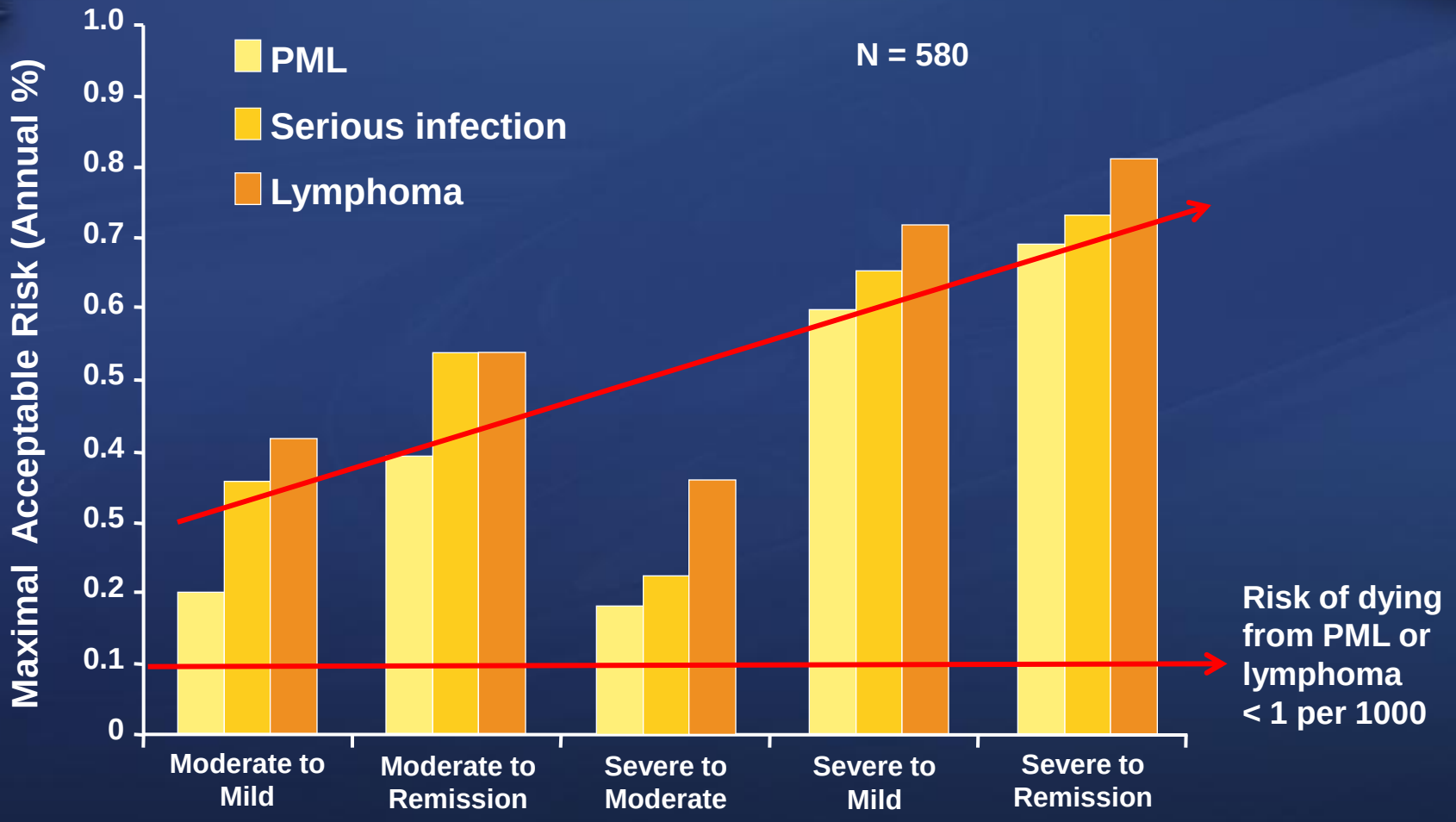
Car accident →

Cancer →

Heart disease →

Odds of Dying, National Safety Council. Available at: http://www.nsc.org/lrs/statinfo/odds.htm. Accessed July 22, 2006.

# Most patients are willing to take these risks




Johnson et al. *Gastroenterology* 2007.

# 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