

Balancing the Risks and Benefits of Treatment

for Inflammatory
Bowel Diseases

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Balancing The Risks And Benefits Of Treatment For Inflammatory Bowel Diseases

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The Inflammatory Bowel Diseases (IBD) Medicine Cabinet

- 5-Aminosalicylates (5-ASAs)
 - Balsalazide (Colazal[®]), mesalamine (Asacol[®], Lialda[®], Pentasa[®]), sulfasalazine (Azulfidine[®])
- Antibiotics
 - Ciprofloxacin (Cipro[®]), metronidazole (Flagyl[®])
- Corticosteroids
 - Hydrocortisone, methylprednisolone (Solu-Medrol[®]), prednisone
 - Budesonide (Entocort[®])
- Immunomodulators (IMs)
 - 6-Mercaptopurine (6MP), azathioprine (Azasan[®], Imuran[®])
 - Methotrexate
- Biologics
 - Adalimumab (Humira[®]), certolizumab pegol (Cimzia[®]), infliximab (Remicade[®]), natalizumab (Tysabri[®])

Topics To Be Reviewed

- Benefits and risks of immunomodulators
- Benefits and risks of biologics
- Learning and making trade-offs
- Decoding the numbers game

Immunomodulators

- Also called “immune suppressants” or “antimetabolites”
- Search the Internet responsibly – they were used for years as “chemotherapy”
- Have been used since the 1970s for the treatment of IBD
- They work by quieting down the immune system

What is the Efficacy of 6-Mercaptopurine/Azathioprine (6MP/AZA)?

- These medications can take 2–4 months to fully “kick-in”
- Usually taken along with another medication to get patients into remission
- Once in remission, about 70% (70 out of 100) of patients stay in remission for at least one year

What Are the Main Side Effects of 6MP/AZA?

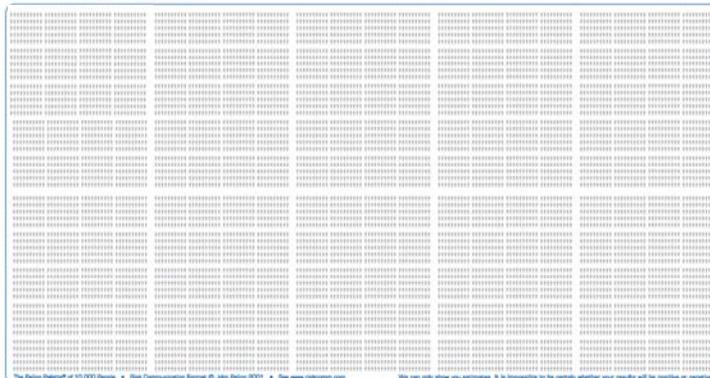
Event	Estimated Frequency (annual)
Allergic reactions	3% (3/100)
Pancreatitis	3% (3/100)
Serious infection	5% (5/100)
Death from serious infection (sepsis)	0.15% (15/10,000)
Non-Hodgkin lymphoma (NHL)	0.04% (4/10,000)
Death from lymphoma	0.01%–0.02% (1–2/10,000)

Siegel CA. *Practical Gastroenterology*. 2007;XXXI:14-24.

A Risk Palette

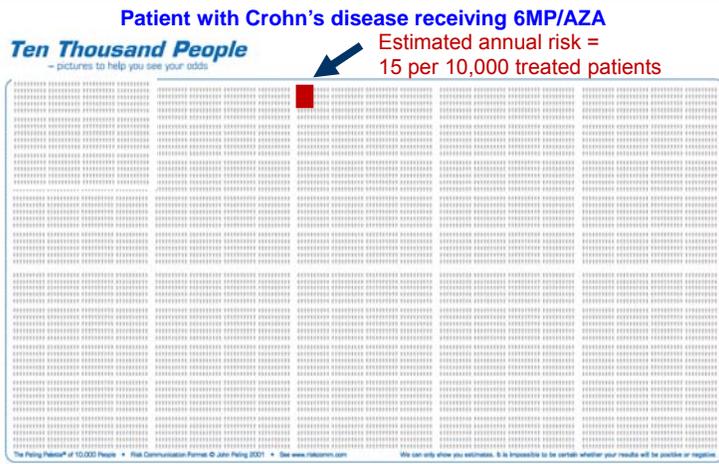
Read as: if 10,000 people were treated with drug X for 1 year, we would expect this many people to _____

Ten Thousand People
— pictures to help you see your odds



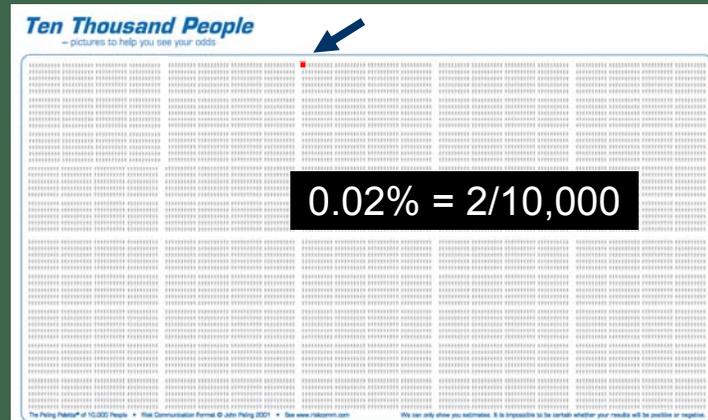
The Risk Palette of 10,000 People • Risk Communication Forum © John Peleg 2007 • See www.fda.gov/cder
We can only show you estimates. It is impossible to be certain whether your results will be positive or negative.

Risk of Dying From a Serious Infection



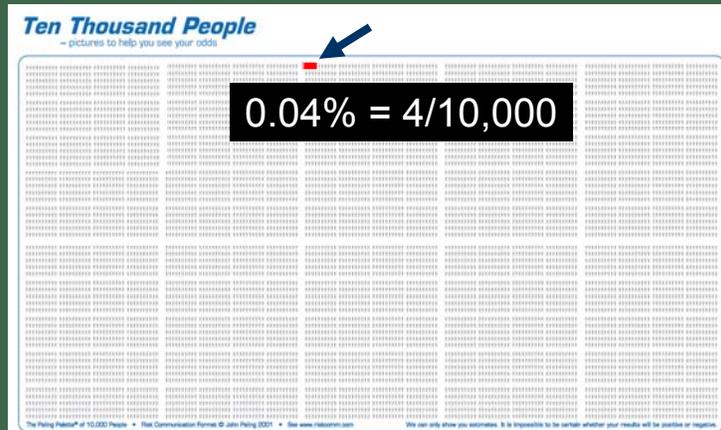
Pearson DC, et al. *Ann Intern Med.* 1995;123:132-142.

Annual Risk for Developing NHL in the US



Surveillance, Epidemiology, and End Results (SEER) Database, 2007.

Annual Risk for Developing NHL While On 6MP/AZA



Siegel CA, et al. *Clin Gastroenterol Hepatol*. 2009.

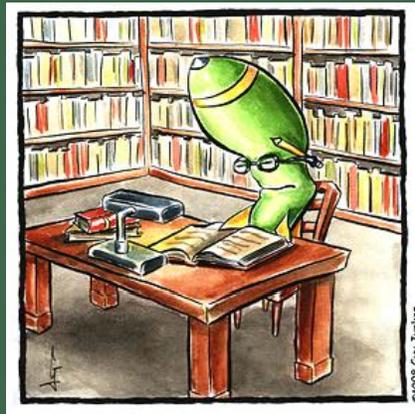
Topics To Be Reviewed

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- Benefits and risks of biologics
- Learning and making tradeoffs
- Decoding the numbers game

What Is Biologic Therapy?

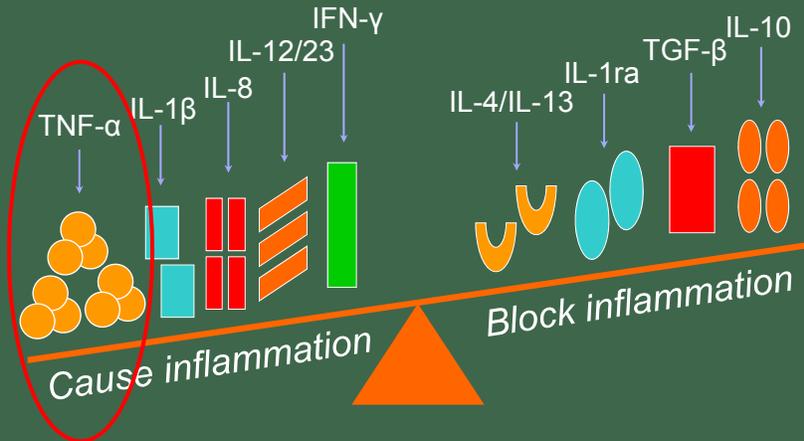
- Technical Answer
 - Biologic therapy is any therapy (medication) that is made from living organisms (humans, other animals, bacteria, plants)
 - The medication is similar or identical to the actual biologic chemicals that our body makes
- Practical answer for IBD
 - Designer drugs made to specifically *block* inflammation or *stimulate* anti-inflammatory processes

Smart Bomb



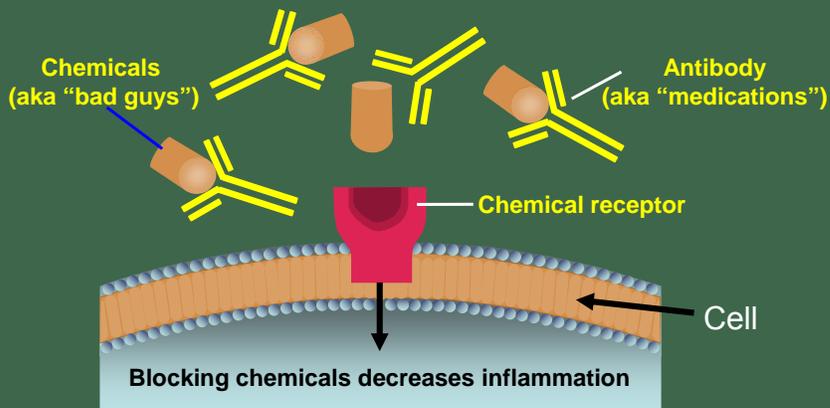
While the other explosives played during recess, Charlie studied diligently in hopes of one day becoming a Smart Bomb.

IBD Biologic Treatment Made Simple



IFN=interferon; IL=interleukin; IL-1ra=interleukin 1 receptor antagonist; TGF=transforming growth factor; TNF=tumor necrosis factor.

The Antibodies (Medications) Block Chemicals That Cause Inflammation



Adapted from Choy EHS, Panayi GS. *N Engl J Med.* 2001;344:907-916.

Is There a Difference Between the Available Biologics?

- Infliximab, adalimumab and certolizumab pegol are all *anti-TNF drugs*
 - Infliximab → Intravenous every 8 weeks
 - Adalimumab → Subcutaneous injection every 2 weeks
 - Certolizumab → Subcutaneous injection every 4 weeks
- Natalizumab is an antiadhesion molecule
 - Recently approved by the US FDA
 - Natalizumab → Intravenous infusion every 4 weeks
 - TOUCH™ (Tysabri Outreach: Unified Commitment to Health) program

How Effective Is Treatment With Anti-TNF Therapy? (Adalimumab, Certolizumab, Infliximab)

Within a few weeks of starting treatment with an anti-TNF drug:

40% (40/100) did not have an improvement in their symptoms

60% (60/100) had an improvement in their symptoms

Results based on a weighted average from PRECISE 2 (only response included since 6-month endpoint), ACCENT1, and CHARM studies.

How Effective Is Treatment With Anti-TNF Therapy?

(Adalimumab, Certolizumab, Infliximab)

Within a few weeks of starting treatment with an anti-TNF drug:

40% (40/100) did not have an improvement in their symptoms

60% (60/100) had an improvement in their symptoms

Continued anti-TNF or placebo

For those who improved, after 1 year of either continued treatment with the anti-TNF medication or with placebo, this is what happened:

	Anti-TNF	Placebo
How many people were free from symptoms of Crohn's disease?	34% 34 in 100	13% 13 in 100

Results based on a weighted average from PRECISE 2 (only response included since 6-month endpoint), ACCENT1, and CHARM studies.

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

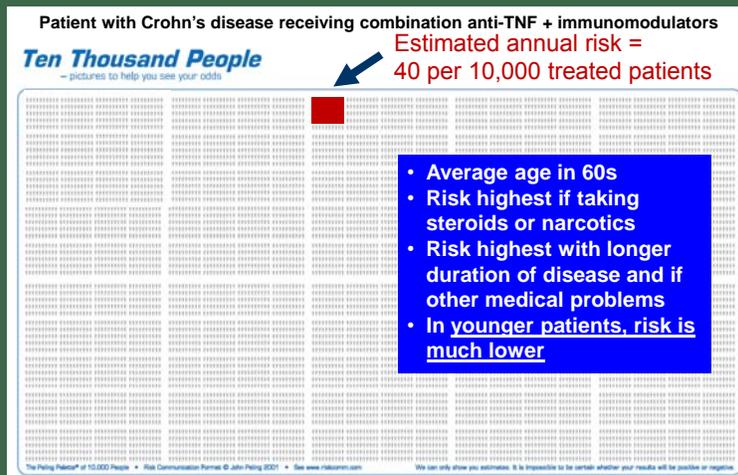
The Main Side Effects of Anti-TNF Treatment

If 10,000 patients were treated for one year

Event	Estimated Frequency
NHL(baseline)	2/10,000
NHL (on IMs)	4/10,000
NHL (on anti-TNF)	6/10,000
Hepatosplenic T-cell lymphoma	Unknown
Death from sepsis (lower for younger patients)	4/1000
Tuberculosis	5/10,000

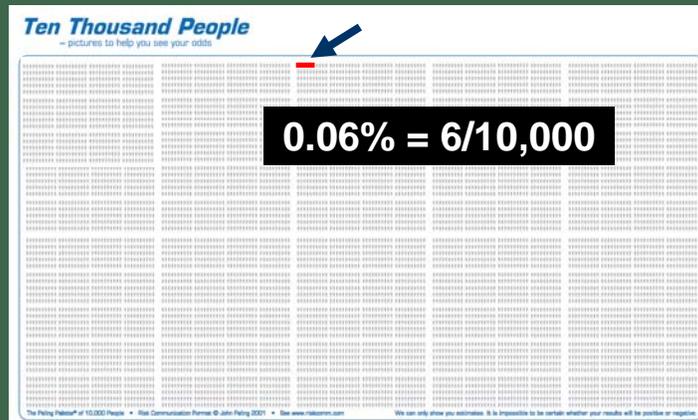
Adapted from Siegel CA. In *Inflammatory Bowel Disease: Translating Basic Science Into Clinical Practice*. In press, 2008.

Risk of Dying From a Serious Infection



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

Annual Risk for NHL While Taking an Anti-TNF + IM



Siegel CA, et al. *Clin Gastroenterol Hepatol*. 2009.

What is Hepatosplenic T-cell Lymphoma?

- A type of NHL
- Symptoms and signs
 - Fevers, chills, night sweats that do not go away
 - Enlarged liver and spleen
 - Low blood counts
- Diagnosis made by biopsy of the liver, spleen or bone marrow
- Particularly nasty type of cancer that is difficult to treat

What Does Hepatosplenic T-cell Lymphoma Have To Do With IBD?

- Reported in patients taking azathioprine
 - 9 cases reported
- Reported in patients taking infliximab + azathioprine or 6MP
 - 16 cases reported
 - Young people (average age 23)
 - Most are male
- Out of *a lot* of patients
 - About 400,000 IBD patients treated with infliximab
 - Over 1 million patients treated with infliximab for all different uses worldwide

Centocor, Inc. Data on file. 2009.

Natalizumab

- A new way of treating Crohn's disease
- Also used to treat multiple sclerosis
- Only used for patients who have failed an anti-TNF agent
- Concern about a serious neurologic problem called progressive multifocal leukoencephalopathy (PML)

Treatment With Natalizumab

Patients who have failed anti-TNF therapy

After 10 weeks of treatment with natalizumab

	Natalizumab	Placebo
How many patients had <u>improvement</u> of symptoms of Crohn's disease?	51% 51 in 100	41% 41 in 100

Results based on a data from ENACT 1 and 2.
Sandborn WJ, et al. *N Engl J Med.* 2005;353:1912-1925.

Treatment With Natalizumab

Patients who have failed anti-TNF therapy

After 10 weeks of starting treatment with natalizumab

	Natalizumab	Placebo
How many patients had <u>improvement</u> of symptoms of Crohn's disease?	51% 51 in 100	41% 41 in 100



Of those who improved, after 15 months of continued treatment with either natalizumab or placebo, this is what happened:

	Natalizumab	Placebo
How many patients were <u>free from symptoms</u> of Crohn's disease?	47% 47 in 100	18% 18 in 100

Results based on a data from ENACT 1 and 2.
Sandborn WJ, et al. *N Engl J Med.* 2005;353:1912-1925.

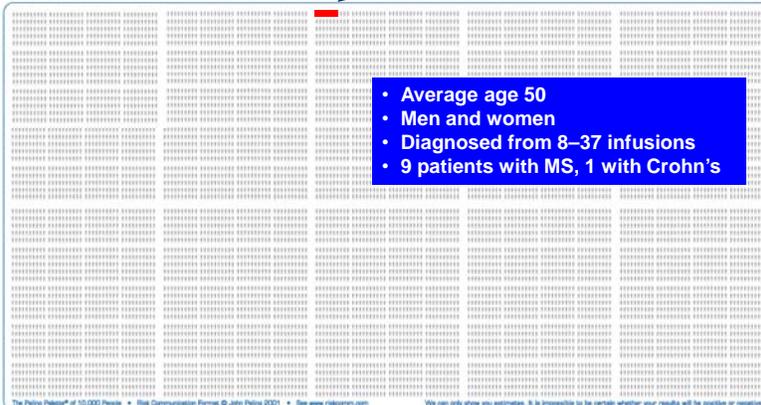
Natalizumab

- Ten cases of JC virus–related PML in the world
 - Nine patients with multiple sclerosis (MS)
 - One patient with Crohn's disease
- As of April 2009
 - > 52,000 patients have received natalizumab
 - > 6,800 patients have been treated for longer than 2 years
- What are the other options?
 - Surgery, clinical trials

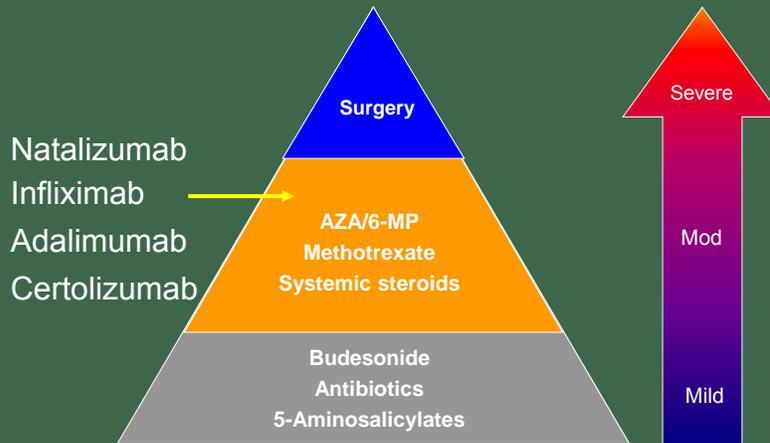
Elan Pharmaceuticals. Data on file, 2009.

Estimated Risk for Developing PML

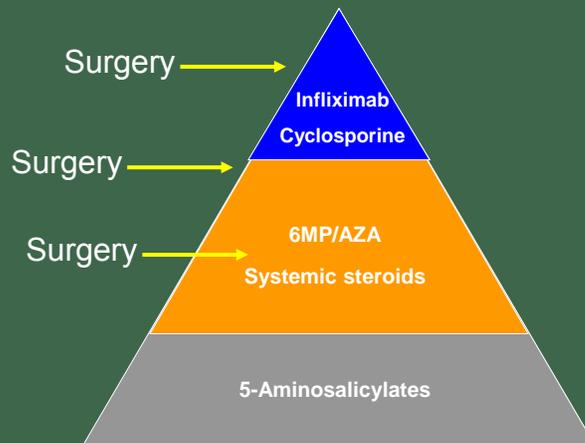
If 10,000 patients were treated with natalizumab for 1 year
Ten Thousand People **Estimated annual risk =**
– pictures to help you see your odds. **7 per 10,000 treated patients**



Treatment Pyramid for Crohn's Disease



Treatment Pyramid for Ulcerative Colitis



Are Two Drugs Better Than One for Crohn's disease?

- A recent research study was performed to test whether treatment was more effective with
 - Azathioprine alone
 - Infliximab alone
 - A combination of azathioprine *and* infliximab

After 6 Months of Treatment

	Azathioprine	Infliximab	Combination
How many people were free from symptoms and off of prednisone?	31% 32 in 100	44% 44 in 100	57% 57 in 100
How many had a completely normal colonoscopy after treatment?	17% 17 in 100	30% 30 in 100	44% 44 in 100
Serious side effects	Equal across the groups		

**But, some side effects may occur more often with 2 drugs.
 Which would you prefer?**

Topics To Be Reviewed

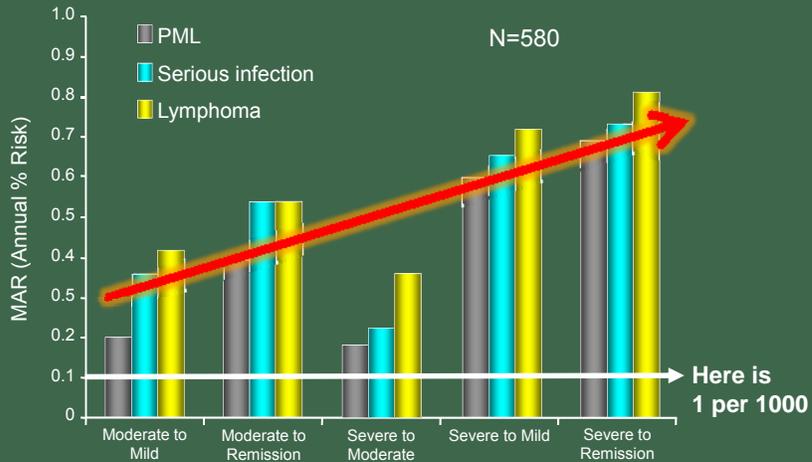
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Risks Associated With IBD

- If IBD is not controlled it usually leads to surgery
 - Chance of requiring surgery for Crohn's disease
 - Within 1 year of diagnosis: 40%
 - Within 5 years of diagnosis: 50%
 - Within 20 years of diagnosis: 80%
 - Chance of requiring surgery (colectomy) for ulcerative colitis
 - Within 20 years of diagnosis: 20%

Cohen RD. *Aliment Pharmacol Ther.* 2002;16:1603-1609.
Gregor JG, et al. *Inflamm Bowel Dis.* 1997;3:265-276.
Munkholm P, et al. *Gastroenterology.* 1993;105:1716-1723.
Hutfless SM, et al. *Gastroenterology.* 2007;133:1779-1786.

Patients' Willingness to Take Risk



MAR=maximum acceptable risk.
Johnson FR, et al. *Gastroenterology*. 2007;133:769-779.

Putting Risk in Perspective

- Over a lifetime, the chance of dying from
 - Lightning: 1 out of 80,000
 - Bicycling accident: 1 out of 5,000
 - Drowning: 1 out of 1,000
 - Car accident: 1 out of 261
 - Cancer: 1 out of 8
 - Heart disease: 1 out of 5

National Safety Council. Available at: www.nsc.org/research/odds.aspx. Accessed April 21, 2009.

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- Benefits and risks of immunomodulators
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This Is Doctor Talk

Not very useful to help make a decision about treatment

0.01%

SIR = 3.23

RR = 1.48

NNT = 7

Common

P < 0.05

OR = 14.5

Rare

This Is Doctor Double-Talk

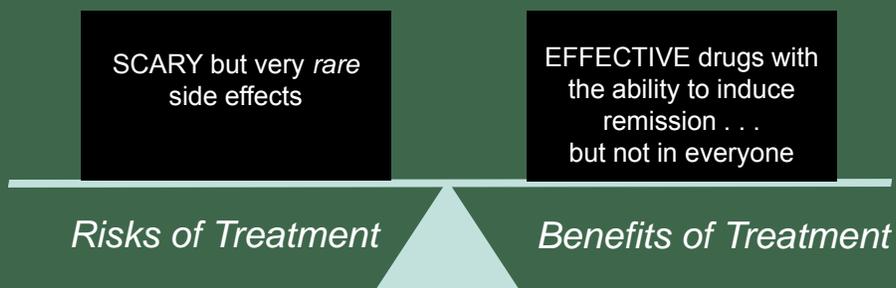
- “Framing” is the term used to present the same results in different ways^{1,2}
 - Relative risk = 34% reduction in heart attacks
 - Absolute risk = 1.4% reduction in heart attacks
 - Number needed to treat = 71

All show that treatment decreases chance of heart attack from 4.1% → 2.7%

1. Malenka DJ, et al. *J Gen Intern Med.* 1993;8:543-548.
2. Hux JE, Naylor CD. *Med Decis Making.* 1995;5:152-157.

Weighing the Risks Against the Benefits

It is an individual decision . . . but also keep in mind the risks of “under-treating” the disease



Summary

- Immunomodulator and biologic medications can dramatically improve the quality of life in IBD
- There are some very serious, but very rare side effects associated with these medications
- If you need the medication, the benefits most likely outweigh the risks
- Clearly understand the trade-offs so that you can make a decision that is right for you

Life Is Full of Risks, and Some Are Worth Taking



Thank You