


Safety Issues in IBD: Discussing Treatment Risks with Your Patients

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WARNING


RISK OF INFECTIONS

Patients treated with REMICADE are at increased risk for infections, including progression to serious infections leading to hospitalization or death (see CONTRAINDICATIONS AND WARNINGS). These infections have included bacterial sepsis, tuberculosis, invasive fungal and other opportunistic infections. Patients should be educated about the symptoms of infection, closely monitored for signs and symptoms of infection during and after treatment with REMICADE, and should have access to appropriate medical care. Patients who develop an infection should be evaluated for appropriate antimicrobial therapy and for serious infections REMICADE should be discontinued.

Tuberculosis (frequently disseminated or atypical presentation) has been observed in patients receiving REMICADE. Patients should be evaluated for tuberculosis risk factors and be treated for latent tuberculosis infection (LTBI) before initiating REMICADE and during therapy. Treatment of latent tuberculosis infections should be initiated prior to therapy with REMICADE. Treatment of latent tuberculosis in patients with a reactive tuberculin test reduces the risk of tuberculosis reactivation in patients receiving REMICADE. Some patients who tested negative for latent tuberculosis prior to receiving REMICADE have developed active tuberculosis. Physicians should monitor patients receiving REMICADE for signs and symptoms of active tuberculosis, including patients who tested negative for latent tuberculosis infection.

HEPATITIS B, C, AND T. SPOROZOITES

Some postmarketing cases of hepatitis B, T-cell lymphoma have been reported in adolescent and young adult patients with Crohn's disease treated with REMICADE. This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal. All of these hepatocellular T-cell lymphomas with REMICADE have occurred in patients on concomitant treatment with azathioprine or 6-mercaptopurine.



The IBD Medicine Cabinet

- **5-Aminosalicylates (5-ASAs)**
 - Sulfasalazine (Azulfidine), Mesalamine (Asacol, Pentasa, Lialda), Balsalazide (Colazal)
- **Antibiotics**
 - Ciprofloxacin (Cipro), Metronidazole (Flagyl), Rifaximin (Xifaxan)
- **Corticosteroids**
 - Prednisone, Solumedrol, Hydrocortisone
 - Entocort
- **Immunomodulators**
 - Azathioprine (Imuran, Azasan), 6-mercaptopurine (6MP)
 - Methotrexate
- **Biologics**
 - Infliximab (Remicade), Adalimumab (Humira), Certolizumab pegol (Cimzia), Natalizumab (Tysabri)

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

If 10,000 patients were treated for 1 year

Event	Estimated Frequency (annual)
Having an Allergic reactions	3% (3/100)
Getting Pancreatitis	3% (3/100)
Getting a Serious Infection	5% (5/100)
Dying from Serious Infection (sepsis)	0.15% (15/10,000)
Getting Non-Hodgkin Lymphoma	0.04% (4/10,000)
Dying from Lymphoma	0.01%-0.02% (1-2/10,000)

Siegel, CA. Practical Gastroenterology 2007; XXXI (11): 14-24.

Side-effects of anti-TNF agents

- Headache, nausea
- Rash
- Hypersensitivity reactions
 - infusion or injection site reactions
 - serum sickness/delayed hypersensitivity
- Immunogenicity
- Infections
 - mild and serious
- Demyelinating disorders
- Psoriasis
- Autoantibodies
- Pancytopenia
- Heart failure
- Hepatotoxicity
- Malignancy

Adverse Reactions Associated with anti-TNF Treatment

Event	Estimated Frequency
Nausea, headache	About the same as placebo
Infusion or injection site reactions	3%-20%
Delayed hypersensitivity reactions	1%
Drug related lupus	1%
Multiple sclerosis, heart failure, serious hepatic toxicity	Case Reports

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

Who are the patients who are most at risk for serious infections?

- 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 less at risk

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

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

Risk of NH Lymphoma with anti-TNF + IM treatment for Crohn's Disease Meta-analysis Results

- 8905 patients representing 21,178 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)

	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

Siegel et al, CGH 2009;7:874.

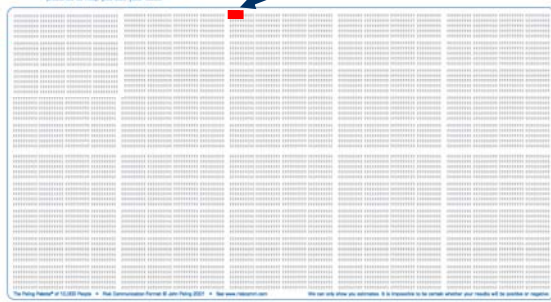
*not reported in 2

Risk of Developing NH Lymphoma

Patient receiving anti-TNF + Immunomodulator Therapy for 1 year

Ten Thousand People → probability for finding you are your odds

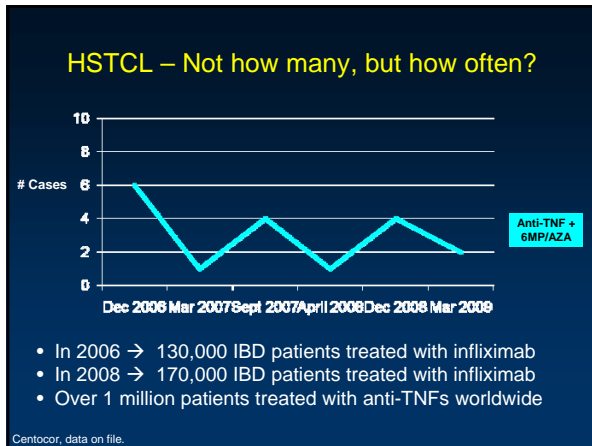
Risk with combination therapy



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.



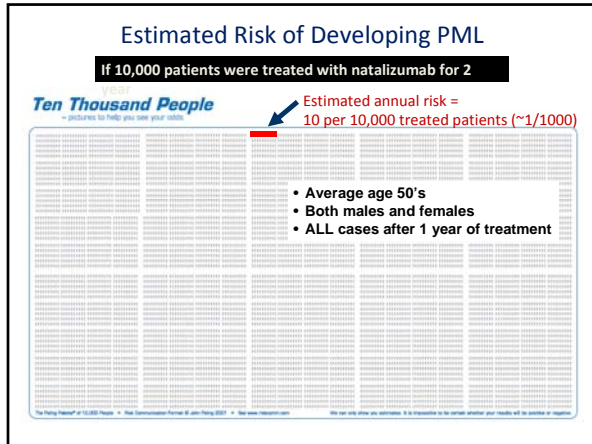
Risks of Serious Side-Effects with anti-TNFs

If 10,000 patients were treated with anti-TNF for one year...

Event	Estimated Frequency
Non-Hodgkin Lymphoma (baseline)	2/10,000
Non-Hodgkin Lymphoma (on IM)	4/10,000
Non-Hodgkin Lymphoma (on anti-TNF)	6/10,000
Hepatosplenic T-cell Lymphoma	Unknown
Death from sepsis (if older, with co-morbidities & steroids)	40/10,000
Tuberculosis	5/10,000

Adapted from Siegel CA. Comprehensive approach to patient risk. Risk versus benefit of biologics and immune suppressants. In: Targan S, Shanahan F, Karp L, eds. Inflammatory bowel disease: Translating basic science into clinical practice. In press, 2007.

- ### Natalizumab
- 26 cases of JC virus related progressive multifocal leukoencephalopathy
 - 25 patients with multiple sclerosis
 - 1 patient with Crohn's disease
 - As of early 2009
 - > 60,000 pts have received natalizumab
 - > 13,000 pts have been treated for longer than 2 years
 - What are the other options?
 - Surgery, clinical trials
- Klein-Schmidt-DeMasters BK, Tyler KL. N Engl J Med. 2005;353:389-374; Langer-Gould A et al. N Engl J Med. 2006;353:375-381; Van Assche G et al. N Engl J Med. 2005;353:362-368; Sands et al. Gastro 2008;134:A206; Sandborn et al. NEJM 2005; Targan et al. Gastro 2007;



Compared to what?

What puts patients at the most risk?

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 Steroids and Immunomodulators

- 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

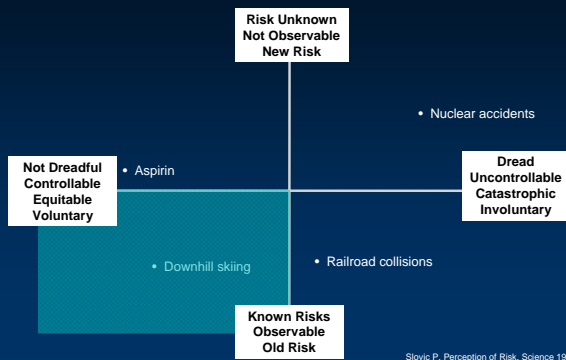
Lewis et al, AJG 2008;103:1428.

What is risk anyway?

Risk = probability x consequence



Factors controlling risk perception



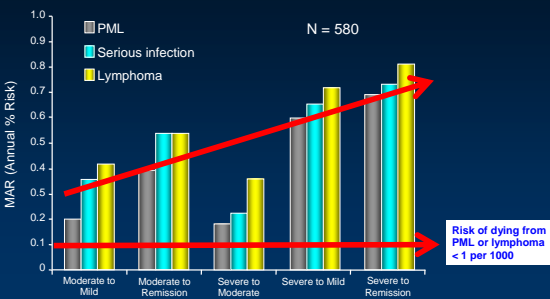
Slovic P. Perception of Risk. Science 1987.

How Much Risk are Crohn's Patients Willing to Accept?

- Web-based survey of 580 patients with Crohn's disease
- Conjoint trade-off analysis
- Evaluated patients' willingness to accept the risk of treatment related side-effects in exchange for improvement in daily symptoms

Johnson et al. Gastroenterology 2007.

Patient Willingness to Take Risk



Johnson et al. Gastroenterology 2007.

How to Communicate All of This to Patients?

0.01%
SIR = 3.23
NNT = 7
OR = 14.5
RR = 1.48
P < 0.05
Common
Rare

Berry et al. Drug Saf. 2003;26:1

Fair and Clear Communication of Risks and Benefits

- Numeracy (quantitative literacy)¹
 - 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

1. Schwartz LM et al. Ann Intern Med. 1997 Dec 1;127(11):966-72.

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

BOTH show that treatment decreases chance of Heart Attack from 4.1% → 2.7%

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

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

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

Summary: Risks & Benefits

- Immunomodulators and biologics are associated with real, but small risks of serious adverse events
- Risk perception is variable
- Patients are willing to accept risk, as long as there is substantial benefit
- Clear communication to patients is critical
