Balancing the Risk and Benefit of Immunomodulator and Biologic Therapy in Patients with IBD

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Determining Relationship of Adverse Effects to Medication

- Expected occurrence in general population
- Disease-specific expected occurrence
- Risk determinants within disease
- Characteristics of the adverse events
- Relative risk of reoccurrence
- Benefit/risk determinations and alternative treatment options

Safety

- Immunomodulators
- Methotrexate
- AntiTNF Therapy
## TPMT Pharmacogenetics

### Genotype–Phenotype Relationship

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Frequency</th>
<th>Enzyme Activity</th>
<th>Alleles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homozygous Normal</td>
<td>89%</td>
<td>normal to high</td>
<td>TPMT(^H)/TPMT(^H)</td>
</tr>
<tr>
<td>Heterozygous</td>
<td>11%</td>
<td>intermediate</td>
<td>TPMT(^H)/TPMT(^L)</td>
</tr>
<tr>
<td>Homozygous Deficient</td>
<td>0.3%</td>
<td>low to absent</td>
<td>TPMT(^L)/TPMT(^L)</td>
</tr>
</tbody>
</table>


## TPMT: Is Testing Cost Effective?

Assumptions: 3% develop leukopenia, homozygous mutant 0.3%, heterozygous mutant 11%

Adapted from J Winter et al. Aliment Pharm Ther 2004;20:593-9
TPMT: Is Testing Cost Effective?

1000 Patients

No benefit from testing

30 With Leukopenia

9970 Without Leukopenia

20 Wild Type

7 Heterozygotes

3 Homozygotes

9867 Wild Type

103 Heterozygotes

Assumptions: 3% develop leukopenia, homozygous mutant 0.3%, heterozygous mutant 11%

Adapted from J Winter et al. Aliment Pharm Ther 2004;20:593-9

TPMT genotype associated with early but not late severe myelosuppression

Myelosuppression with Thiopurines

Timing of Myelosuppression

- Early severe leukopenia preceded by mild leukopenia in 5/6

Common Adverse Events with AZA / 6MP

- 396 patients, mean duration of treatment 33.6 months, mean follow-up 60.3 months
- Toxicity
  - Pancreatitis: 13 (3.3%)
  - Bone marrow depression: 8 (2.0%)
  - Allergic reaction: 8 (2.0%)
  - Drug induced hepatitis: 1 (0.3%)
  - Infection: 29 (7.4%)
  - Neoplasm: 12 (3.1%)

Risk of Lymphoma with AZA / 6-MP Use

- 18 studies (among 4383 citations) met inclusion criteria.
- The SIR for lymphoma was
  - Overall: 4.92 (95% CI, 3.10–7.78),
  - 2.80 (95% CI, 3.10–7.78) in 8 population studies
  - 9.24 (95% CI, 4.69–18.2) in 10 referral studies.
- Population studies demonstrated an
  - Increased risk among current users (SIR=5.71; 95% CI, 3.72–10.1) but
  - No increased risk in former users (SIR=1.42; 95% CI, 0.86–2.34).


Risk of Lymphoma with AZA / 6-MP Use

- Risk Became Significant after One year of exposure
- Sex*
  - Men have a greater risk than women (RR = 1.98; P < .05)
  - Both sexes were at increased risk for lymphoma
    - Men: SIR for men = 4.50 (95% CI 3.71–5.40)
    - Women: SIR for women = 2.29 (95% CI 1.69–3.05)
- Age
  - Age 30-59: 1 lymphoma per 2000 pt-yrs of followup
  - Patients < 30 years had the highest RR
    - SIR=6.99 (CI, 95% CI,2.99–16.4)
    - Younger men had the highest risk: Men < 30 : SIR~ 9
  - The absolute risk was highest in patients > 50 years 1.354 cases per patient–year
    - RR=4.78
- *- subanalysis of 2 studies

Hepatosplenic T-Cell Lymphoma (HSTCL) in Patients with IBD

- Rare form of lymphoma
  - *200+ reports in the literature*
  - Post-organ transplant

Inflammatory Bowel Disease: N=36 total
- AZA alone: N=16
- Anti TNF: N=20
- N=18: infliximab: All with current or prior AZA
- N=2: adalimumab: All with prior infliximab
- All patients who received AZA
  - All but 1 patient had >2 years of AZA use


The Impact of Age-specific Risks of Lymphoma on the Decision to Use Combination Therapy (IFX and AZA) Versus IFX Alone: A Markov Model (cont’d)

- Take-home Messages
  - From ages 35 to 65, combination therapy is the preferred strategy
  - For those who are >65, and particularly those >75, monotherapy may be a more beneficial strategy due to the increased risk of NHL and NHL-related mortality with combination therapy
  - Due to HSTCL risk, combination therapy in young males may result in more deaths without providing substantially greater QALYs

HSTCL = hepatosplenic T-cell lymphoma; QALYs = quality-adjusted life-years

Scott FI, et al. Paper presented at: Digestive Disease Week; May 3-6, 2014; Chicago, IL
Toxicities

- Immunomodulators
- Methotrexate
- AntiTNF Therapy

Methotrexate Toxicity

- Rash, alopecia
- Nausea, mucositis, diarrhea
  - Folate mitigates much of this
  - Ondansetron before MTX injections
- Bone marrow suppression
- Hypersensitivity pneumonitis
- Increased LFTs
- Hepatic fibrosis/cirrhosis
MTX Hepatotoxicity

- Risk factors:
  - Obesity
  - Alcohol
  - Diabetes
- Screen for HBC/HCV
- Monitor LFTs, adjust dose accordingly
  - Steatosis, steatohepatitis, hepatic fibrosis
  - Fortunately, risk of hepatotoxicity is low (0.9-1.4 per 100 person-months)


MTX Pulmonary Toxicity

- Approximately 2-7% of treated patients
- Various forms
  - Hypersensitivity pneumonia
  - BOOP
  - Interstitial pneumonia
  - Pleuritis / effusion
- Risk factors
  - Age > 60
  - RA with pulmonary
  - Low albumin
  - Diabetes
- Can present as culture negative pneumonia
- Subacute dry cough with dyspnea
- Up to 50% have peripheral eosinophilia
- Abnl PFTs in subacute presentation: restrictive pattern, ↓DLCO
- Sometimes BAL ± lung bx needed
- Rx: hold MTX, consider steroids
  - Clinical improvement within days and radiographic improvement within weeks

D’Andrea N et al, Multidisciplinary Respiratory Medicine 2010; 5(5): 312-319
Toxicities

- Immunomodulators
- Methotrexate
- AntiTNF Therapy

Major Toxicities

- Neurologic
- Infection
- Immunologic
- Dermatologic
- Malignancy
Safety Issues With Anti-TNF Therapy

- Infection and malignancy
  - Black-box warning for serious infection and malignancy for all anti-TNF therapies\(^1\)-\(^3\)
  - Black-box warning for HSTCL (ADA and IFX)\(^1\),\(^2\)
- Reactivation of hepatitis B\(^4\)
- Skin cancer\(^4\)
- Psoriasis\(^4\)
- Autoimmunity (lupus-like syndrome <1%)\(^4\)
- Immunogenicity—antibodies to anti-TNF\(^4\)
- Demyelinating disorders, CHF, liver toxicity\(^4\)

Abbreviation: CHF, congestive heart failure; HSTCL, hepatosplenic T-cell lymphoma.


Anti-TNF & Demyelinating Diseases

- CNS TNF\(\alpha\) levels increased in active multiple sclerosis
- Case reports of exacerbation/onset of MS, demyelination, and optic neuritis among patients treated with anti-TNF\(\alpha\) meds
- Lanercept trial stopped early - active treatment group more exacerbations
Anti-TNF & Demyelinating Diseases

• Increased incidence in patients with IBD
• Not clearly medication or disease severity related
• Anti-TNF medications contraindicated in patients with MS

Anti-TNF Rx & Demyelinating Diseases

- GPRD:
  - Retrospective cross-sectional study using 1988 to 1997 data
  - 7988 CD & 12,185 UC pts matched for age, sex, and primary care practice to 80,666 randomly selected controls.

<table>
<thead>
<tr>
<th>Table 2. Association Between IBD and Demyelinating Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control’s disease, odds ratio (95% CI)</td>
</tr>
<tr>
<td>MS or demyelination</td>
</tr>
<tr>
<td>MS</td>
</tr>
<tr>
<td>ON</td>
</tr>
<tr>
<td>MS/ON</td>
</tr>
</tbody>
</table>

Note: Demyelinating diseases include MS, demyelination, or ON.

<table>
<thead>
<tr>
<th>Table 3. Association Between IBD and MS/ON Stratified by Smoking Status and Recent Use of Immunosuppressive Therapies for IBD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control’s disease, odds ratio (95% CI)</td>
</tr>
<tr>
<td>Mediation use†</td>
</tr>
<tr>
<td>Treated with AZA/6MP</td>
</tr>
<tr>
<td>No treatment with AZA/6MP</td>
</tr>
<tr>
<td>Treated with corticosteroids</td>
</tr>
<tr>
<td>No treatment with corticosteroids</td>
</tr>
<tr>
<td>Smoking status</td>
</tr>
<tr>
<td>Smokers</td>
</tr>
<tr>
<td>Nonsmokers</td>
</tr>
<tr>
<td>Unknown</td>
</tr>
</tbody>
</table>

†Use of Immunosuppressive therapies for IBD was classified as ever exposed or never exposed during the period of up to standard data entry.

Major Toxicities

- Neurologic
- Infection
- Immunologic
- Dermatologic
- Malignancy

Corticosteroids: Infection risk

- Serious infections: TREAT registry
  - Adj OR 2.2 (1.5-3.3), p=0.001
- Opportunistic infection: Mayo Clinic
  - OR 3.3 (1.8-6.1), p<0.001
- Post-operative infections: elective IBD surgery
  - Any infection (29%): OR 3.7 (1.2-11.0)
  - Major infection (20%): OR 5.5 (1.1-27.3)
    - Higher risk with higher dosages used

Lichtenstein GR, et al *Clin Gastro Hepatol* 2006;4:621
Corticosteroids: Risk of Mortality

- Lichtenstein: TREAT
  - Corticosteroid use: \( \text{OR} \ 2.1 \ (1.1-3.8) \ p=0.016 \)
- Lewis: GPRD

| Table 5. Mortality Associated With Current and Recent Immunosuppressant Use |
|-----------------------------------------------------|------------------|---------------------|
| Crohn’s Disease | Ulcerative Colitis |
| Adjusted HR (95% CI)* | Adjusted HR (95% CI)* |
| No use | Reference | Reference |
| Current use | 2.48 (1.85–3.31) | 2.81 (2.26–3.50) |
| Recent use | 1.18 (0.58–2.32) | 2.49 (1.65–3.75) |


AZA/6-MP: Infection Risk

- Post-operative infections
  - Elective surgery for CD/UC
  - Major infection OR=1.2 (95% CI 0.4-4.0)\(^1\)
  - Confirmed in four other studies\(^2\)
- Serious infection
  - TREAT \(^3\) Adj OR 0.8 (95% CI 0.5 – 1.2)
- Opportunistic infections
  - Mayo Clinic (100 with OI vs. 200 no OI) \(^4\)
  - OR = 3.1 (95% CI 1.7 – 5.5)
  - Similar results for MTX

Infliximab & Tuberculosis

- 70 cases of tuberculosis following exposure to infliximab were reported to FDA between licensure in 1998 and May 29, 2001

Anti-TNF Therapy : Infection Risk

Serious Infection: TREAT Registry (1)

- Resistance Mechanism Disorders
  - 3.15 and 3.32 / 100 pt-yrs in placebo- and infliximab-treated IBD patients, respectively

- GI Disorders
  - 0.63 and 1.07 / 100 pt-yrs in placebo- and infliximab-treated IBD patients, respectively

- Respiratory System Disorders
  - 0.94 and 0.97 / 100 pt-yrs in placebo- and infliximab-treated IBD patients, respectively

Are opportunistic infections more common if taking more than 1 medication?

- **Opportunistic infections**

<table>
<thead>
<tr>
<th>Medications</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone, 6MP/AZA, Infliximab</td>
<td></td>
</tr>
<tr>
<td>1 medication</td>
<td>2.9 (1.5–5.3)</td>
</tr>
<tr>
<td>2 or 3 medications</td>
<td>14.5 (4.9–43)</td>
</tr>
</tbody>
</table>

### Combined Use of Immunosuppressive Drugs Increased Risk of Opportunistic Infections

<table>
<thead>
<tr>
<th>Condition</th>
<th>Odds Ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroids alone</td>
<td>2.2 (1.1-4.8)</td>
<td>0.037</td>
</tr>
<tr>
<td>6MP/AZA alone</td>
<td>2.5 (1.2-5.1)</td>
<td>0.015</td>
</tr>
<tr>
<td>IFX alone</td>
<td>11.2 (0.8-153.3)</td>
<td>0.07</td>
</tr>
<tr>
<td>6MP/AZA - steroids</td>
<td>15.7 (4.1-59.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>6MP/AZA - IFX</td>
<td>1.6 (0.1-18.7)</td>
<td>0.71</td>
</tr>
<tr>
<td>6MP/AZA – IFX-steroids</td>
<td>infinite</td>
<td>0.0003</td>
</tr>
</tbody>
</table>


### SONIC Azathioprine + IFX Combination Therapy

**Could it improve the safety of infliximab?**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion reactions</td>
<td>5.6</td>
</tr>
<tr>
<td>Antibodies to IFX</td>
<td>4.9</td>
</tr>
<tr>
<td>Serious Infection</td>
<td>3.9</td>
</tr>
</tbody>
</table>

**Risks in Immunosuppressant Therapy**

- Progressive Multifocal Leukoencephalopathy (PML)
  - *Singh S, et al. IBD 2012*
    - JC Ab negative, +/- prior immunosuppressant therapy: 1:7,099
    - 1:28,397
  - *Bloomgren G, et al. NEJM 2012*
    - JC Ab negative; +/- prior immunosuppressant therapy: 1:7094
  - If JC antibody Negative:
    - Natalizumab treatment selection yield improved outcomes over natalizumab without JC antibody testing or using only a second Anti–TNF antibody agent in all patients (1).


**Summary: Infections**

- Steroids increase risk of most infections in dose dependent manner and also mortality
- AZA/6MP appear to primarily increase the risk of viral infections
- Anti-TNF increase the risk of opportunistic infections (TB, fungal, etc,) and possibly serious infections
- Natalizumab increases the risk of PML and possibly other infections
- Combination therapy likely greater risk than monotherapy
Alternative to AntiTNF Rx

- Corticosteroids
- Natural History

Untreated / Active IBD: Risk of Mortality

Table 3. Mortality Among Patients With Inflammatory Bowel Disease Compared With the General Population

<table>
<thead>
<tr>
<th></th>
<th>Age-, Sex-, and Smoking-Adjusted HR (95% CI)</th>
<th>Fully Adjusted HR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crohn’s disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>1.48 (1.28–1.72)</td>
<td>1.48 (1.28–1.72)</td>
</tr>
<tr>
<td>Mild disease</td>
<td>1.34 (1.13–1.59)</td>
<td>1.27 (1.07–1.51)</td>
</tr>
<tr>
<td>Severe disease</td>
<td>2.17 (1.65–2.86)</td>
<td>2.44 (1.84–3.25)</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>1.20 (1.09–1.33)</td>
<td>1.08 (0.97–1.19)</td>
</tr>
<tr>
<td>Mild disease</td>
<td>1.05 (0.93–1.17)</td>
<td>0.97 (0.87–1.09)</td>
</tr>
<tr>
<td>Severe disease</td>
<td>2.26 (1.83–2.78)</td>
<td>1.67 (1.34–2.09)</td>
</tr>
</tbody>
</table>

**Therapeutic Drug Monitoring**

- **Drug Monitoring**
  - **Proactive**
  - **Reactive**
- **Immunogenicity**

**AntiTNF Antibody: Reactive Testing Algorithm**

Secondary loss of response (disease activity confirmed)

- Therapeutic Infliximab / Adalimumab concentration
- AntiDrug Antibody negative
  - Change drug class or surgery
  - Dose escalate
- AntiDrug Antibody positive
  - Low level
    - Consider dose escalation, addition of immunomodulator, or change anti-TNF
  - High level
    - Change to different anti-TNF
- Sub-therapeutic concentration

Adapted from Khanna et al. AP&T 2013;38:447-459.
Is it possible that the future management of IBD patients on monoclonal antibody medication will include proactive levels?

- Algorithm example: adapted from Cheifetz et al. DDW 2014.

Typical protocol for dose adjustment:

- **IFX undetectable**
  - No or low ATI -> Increase IFX by 2.5mg/kg
  - High ATI -> Stop IFX

- **IFX < 5 (detectable)**
  - Increase IFX by 50-100mg (if no/low ATI)

- **IFX 5 – 10**
  - No change

- **IFX > 10**
  - Decrease dose if > 5mg/g or Increase interval if at 5mg/kg

* On 2 occasions


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Therapeutic Drug Monitoring

- **Drug Monitoring**
  - Proactive
  - Reactive
- **Immunogenicity**
ATI Formation Is Lower in Patients on Concomitant IM Therapy

**ACCENT 1 Subanalysis**

Percent ATI(+) Patients According to Treatment Regimen

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>ATI(+) Patients (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No immunomodulators (n=362)</td>
<td>38</td>
<td>0.003</td>
</tr>
<tr>
<td>With immunomodulators (n=152)</td>
<td>11</td>
<td>0.42</td>
</tr>
<tr>
<td>Episodic strategy</td>
<td>11</td>
<td>0.42</td>
</tr>
<tr>
<td>5 mg/kg Maintenance</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>10 mg/kg Maintenance</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>


AAA Formation Lowers Adalimumab Trough Serum Levels

- 92% of the patients with a trough serum concentration measured below the threshold for detection were positive for AAA

<table>
<thead>
<tr>
<th>Therapy</th>
<th>AAA (+)</th>
<th>AAA (-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 4</td>
<td>6.1 (n=58)</td>
<td>2.1 (n=98)</td>
</tr>
<tr>
<td>Week 12</td>
<td>8.9 (n=53)</td>
<td>0.6 (n=58)</td>
</tr>
<tr>
<td>Week 24</td>
<td>8.8 (n=37)</td>
<td>0.1 (n=58)</td>
</tr>
<tr>
<td>Week 54</td>
<td>11.1 (n=46)</td>
<td>0.02 (n=37)</td>
</tr>
<tr>
<td>Therapy</td>
<td>11.1 (n=46)</td>
<td>0.05 (n=30)</td>
</tr>
</tbody>
</table>

**SONIC**

**IFX Trough Levels at Week 30**

Patients who had 1 or more PK samples obtained after their first study agent administration were included in the analysis.

<table>
<thead>
<tr>
<th>Median Serum Trough Levels (μg/ml)</th>
<th>(n=97)</th>
<th>(n=109)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFX + placebo</td>
<td>1.6</td>
<td>3.5</td>
</tr>
<tr>
<td>IFX + AZA</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


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**Factors that Influence the PK of TNF Antagonists**

<table>
<thead>
<tr>
<th>Impact on TNF antagonist PK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of ADAs</td>
</tr>
<tr>
<td>Decreases drug concentration</td>
</tr>
<tr>
<td>Increases clearance</td>
</tr>
<tr>
<td>Worse clinical outcomes</td>
</tr>
<tr>
<td>Concomitant use of</td>
</tr>
<tr>
<td>Immunosuppressives</td>
</tr>
<tr>
<td>Reduces ADA formation</td>
</tr>
<tr>
<td>Increases drug concentration</td>
</tr>
<tr>
<td>Decreases drug clearance</td>
</tr>
<tr>
<td>Better clinical outcomes</td>
</tr>
<tr>
<td>Low serum albumin concentration</td>
</tr>
<tr>
<td>Increases drug clearance</td>
</tr>
<tr>
<td>Worse clinical outcome</td>
</tr>
<tr>
<td>High baseline CRP concentration</td>
</tr>
<tr>
<td>Increase drug clearance</td>
</tr>
<tr>
<td>High baseline TNF concentration</td>
</tr>
<tr>
<td>May decrease drug concentration by increasing clearance</td>
</tr>
<tr>
<td>High body size</td>
</tr>
<tr>
<td>May increase drug clearance</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Males have higher clearance</td>
</tr>
</tbody>
</table>

Important Recent Findings

- High trough levels of infliximab correlated with dermatologic adverse reactions
- Low trough levels correlate with infusion reactions

Psoriatic Lesion: AntiTNF Therapy

Psoriatic Lesion: AntiTNF Therapy


Psoriatic Lesion: AntiTNF Therapy

Psoriatic Lesion: AntiTNF Therapy

Scalp psoriasis and alopecia


Psoriatic Lesion: AntiTNF Therapy

Ungal Psoriasis

Psoriatic Lesion: AntiTNF Therapy

Forearm Psoriasis


Psoriatic Lesion: AntiTNF Therapy

Plantar Psoriasis

## Psoriatic Lesion: AntiTNF Therapy

### Table 3 | Outcomes for published cases of anti-TNF-induced psoriasis in IBD, including 30 new cases

<table>
<thead>
<tr>
<th>Skin site involved</th>
<th>Current series (%)</th>
<th>Case reports 1999-2011 (%)</th>
<th>Rahier (GETAID) (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palmoplantar</td>
<td>8/50 (16)</td>
<td>10/50 (20)</td>
<td>27/60 (45)</td>
<td>60/142 (43)</td>
</tr>
<tr>
<td>Scalp</td>
<td>5/50 (10)</td>
<td>15/50 (30)</td>
<td>40/62 (65)</td>
<td>60/142 (42)</td>
</tr>
<tr>
<td>Face</td>
<td>7/50 (14)</td>
<td>6/50 (12)</td>
<td>n/a</td>
<td>13/10 (13)</td>
</tr>
<tr>
<td>Flexures</td>
<td>6/50 (12)</td>
<td>11/50 (22)</td>
<td>27/62 (44)</td>
<td>44/142 (31)</td>
</tr>
<tr>
<td>Trunk</td>
<td>12/50 (24)</td>
<td>22/50 (44)</td>
<td>11/62 (18)</td>
<td>45/142 (32)</td>
</tr>
<tr>
<td>Response to topical therapy</td>
<td>14/30 (47)</td>
<td>15/56 (27)</td>
<td>25/62 (40)</td>
<td>60/142 (41)</td>
</tr>
<tr>
<td>Switch to 2nd anti-TNF for dem</td>
<td>3/50 (6)</td>
<td>5/56 (9)</td>
<td>19/62 (30)</td>
<td>27/148 (18)</td>
</tr>
<tr>
<td>Recurrence on 2nd anti-TNF</td>
<td>3/6 (50)</td>
<td>5/5 (100)</td>
<td>17/19 (90)</td>
<td>23/27 (85)</td>
</tr>
<tr>
<td>Stop 2nd anti-TNF because of rash</td>
<td>1/3 (33)</td>
<td>4/5 (80)</td>
<td>9/19 (47)</td>
<td>14/27 (52)</td>
</tr>
<tr>
<td>Off anti-TNF for derm reasons at follow-up</td>
<td>7/50 (14)</td>
<td>32/56 (57)</td>
<td>25/62 (40)</td>
<td>64/148 (43)</td>
</tr>
</tbody>
</table>

IBD, inflammatory bowel disease; GETAID, Groupe d’Etude Thérapeutique des Affections Inflammatoires du Tube Digestif; TNF, tumor necrosis factor; dem, dermatological; n/a, data not available.

* Sixty-four cases were reported between 1999 and 2011 but six are excluded because the individual patient data were not available for analysis. Data on the site of the skin rash were available in 50 of the 58 cases.

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## Risk of Melanoma in Patients with IBD

<table>
<thead>
<tr>
<th>Study name</th>
<th>Odds ratio (95% CI)</th>
<th>Odds ratio and 95% CI</th>
<th>Relative weight</th>
<th>Melanoma</th>
<th>Total IBD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bernstein 2001</td>
<td>1.09 (0.50–2.38)</td>
<td>6.26</td>
<td>7</td>
<td>5529</td>
<td></td>
</tr>
<tr>
<td>Ekborn 1991</td>
<td>0.70 (0.25–1.95)</td>
<td>3.94</td>
<td>4</td>
<td>4776</td>
<td></td>
</tr>
<tr>
<td>Jess 2004</td>
<td>2.03 (0.45–9.16)</td>
<td>1.94</td>
<td>3</td>
<td>374</td>
<td></td>
</tr>
<tr>
<td>Winther 2004</td>
<td>1.74 (0.69–3.41)</td>
<td>7.30</td>
<td>9</td>
<td>1161</td>
<td></td>
</tr>
<tr>
<td>Karlen 1999</td>
<td>1.20 (0.44–3.04)</td>
<td>4.15</td>
<td>4</td>
<td>1547</td>
<td></td>
</tr>
<tr>
<td>Persson 1994</td>
<td>1.21 (0.27–5.65)</td>
<td>1.94</td>
<td>3</td>
<td>1251</td>
<td></td>
</tr>
<tr>
<td>Long 2012</td>
<td>1.29 (1.09–1.53)</td>
<td>28.28</td>
<td>62</td>
<td>108,570</td>
<td></td>
</tr>
<tr>
<td>Mollerup 1995</td>
<td>1.20 (0.54–2.88)</td>
<td>5.95</td>
<td>6</td>
<td>5546</td>
<td></td>
</tr>
<tr>
<td>Peyrin-Biroulet 2012</td>
<td>0.64 (0.24–1.70)</td>
<td>4.26</td>
<td>4</td>
<td>15,486</td>
<td></td>
</tr>
<tr>
<td>Yadav 2012</td>
<td>2.31 (1.19–4.50)</td>
<td>8.04</td>
<td>11</td>
<td>839</td>
<td></td>
</tr>
<tr>
<td>Greenstein 1985</td>
<td>5.41 (2.08–14.07)</td>
<td>4.44</td>
<td>5</td>
<td>1961</td>
<td></td>
</tr>
<tr>
<td>Hemminki 2009</td>
<td>1.23 (0.86–1.59)</td>
<td>22.91</td>
<td>61</td>
<td>21,788</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.10 (0.70–1.70)</td>
<td>179</td>
<td>172,837</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Medication Use:
Risk of Melanoma in Patients with IBD

Table 5. Multivariate Analyses of Medication Use and Skin Cancer Outcomes in Patients With IBD, Overall and by CD or UC

<table>
<thead>
<tr>
<th>Medication</th>
<th>Melanoma (OR, 95% CI)</th>
<th>NMSC (OR, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IDD overall</td>
<td>CD</td>
</tr>
<tr>
<td>Any use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-ASA</td>
<td>1.06 (0.77-1.45)</td>
<td>0.99 (0.92-1.08)</td>
</tr>
<tr>
<td>Biologic</td>
<td>1.89 (1.96-3.20)</td>
<td>1.14 (0.95-1.39)</td>
</tr>
<tr>
<td>Thiopurine</td>
<td>1.10 (0.72-1.67)</td>
<td>1.85 (1.96-2.05)</td>
</tr>
</tbody>
</table>

NOTE: Conditional logistic regression models adjusted for health care utilization; comorbidities; any use of 5-ASA, biologic, and thiopurine medications as appropriate; matched characteristics include age (within 2 years), sex, IBD subtype, and health plan region. All values are expressed as adjusted OR (95% CI). Data from IMS Health, Lifelink Health Plan Claims Database, from 1997 to 2009.

*Use assessed in entire population, any one prescription filled with any day supply; biologic defined as infliximab, adalimumab, or certolizumab pegol; thiopurine defined as mercaptopurine or azathioprine; 5-ASA defined as mesalamine, olsalazine, balsalazide, or sulfasalazine.

Source: Lifelink Health Plan Claims Database from 1997-2013


Thiopurines Are Associated With NMSC

Yearly incidence rate per 10,000 patient-years

- <50 Years
- 50-65 Years
- >65 Years


Abbreviation: NMSC, nonmelanoma skin cancer.
What Should We Tell Our Patients?

• All medications associated with adverse events
• Most serious adverse events are extremely rare (e.g. lymphoma, MS)- very low absolute risk
• For most patients, the benefits of standard IBD medications outweigh the risks of the medication or alternative therapies, particularly if the patient responded to the therapy for active disease

What Should We Tell Our Patients?

• Risks may be minimized with appropriate monitoring and dosing
  – PPD, Quantiferon gold, CXR, TPMT
• Need to evaluate treatment algorithms
  – AZA / 6-MP: CBC, CMP q 3 mos. At a minimum
  – MTX: CBC, CMP q 2-4 weeks
  – Anti-TNF Therapy: check TB status initially and annually, HBV,
• Do not fully understand safety of medications until marketed for many years