IBD therapy: Balancing risks and benefits
Maria T. Abreu, MD

Reasons for complications in the established IBD patient

- Complications of the disease
- Complications of the treatment
IBD: Systemic Complications

- Eye inflammation*
- Lower bone density*
- Liver and bile duct inflammation
- Kidney stones
- Subfertility*
- Gallstones
- Ovaries
- Uterus
- Arthritis and joint pains

*Higher incidence in women.

CTE Can Also Be Used to Diagnose Osteoporosis

- Biomechanical CT (BCT) can measure bone mineral density (BMD) and bone strength from non contrast CT images
- Clinical CTE provides hip BMD, T-scores, & clinical classifications comparable to DXA
  - For osteoporosis, CTE Sensitivity = 86%, Specificity = 98%
- Combined with BCT, CTE can identify patients with osteopenia
- Ancillary analysis of CTE exams for BMD & bone strength could improve osteoporosis screening rates in IBD patients and may alter management plans

Plasma 25(OH)-Vitamin D Is Associated With a Reduced Risk of Surgery in IBD

- EMR-derived cohort of patients (n=3,217) assessed for association of 25(OH)-Vitamin D status on subsequent surgery

<table>
<thead>
<tr>
<th>Initial Vitamin D Level</th>
<th>Crohn’s Surgery</th>
<th>OR</th>
<th>UC Surgery</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;30 ng/dL</td>
<td>13%</td>
<td></td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>20-29 ng/dL</td>
<td>21%</td>
<td>1.54 (1.06 – 2.25)</td>
<td>12%</td>
<td>1.13 (0.68 – 1.86)</td>
</tr>
<tr>
<td>&lt;20 ng/dL</td>
<td>24%</td>
<td>1.76 (1.24 – 2.51)</td>
<td>17%</td>
<td>2.10 (1.32 – 3.34)</td>
</tr>
</tbody>
</table>

Follow up Vitamin D examined for normalization and outcome in Crohn’s Disease

<table>
<thead>
<tr>
<th>Follow-Up Vitamin D Level</th>
<th>Surgery</th>
<th>Hospitalizations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not normalized</td>
<td>Normalized</td>
<td>Not Normalized</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.0</td>
<td>0.51 (0.32 – 0.82)</td>
</tr>
<tr>
<td>Adjusted</td>
<td>1.0</td>
<td>0.56 (0.32 – 0.98)</td>
</tr>
</tbody>
</table>

Limitations: no adjustment for severity/phenotype;


Higher Exercise Level May Reduce Risk of Relapse in Patients With IBD

- 1,324 patients in remission identified from the CCFA Partners Cohort
- Remission defined as Short Crohn’s Disease Activity Index <150 or Simple Clinical Colitis Activity Index ≤ 2
  - Active disease after 6 months (relapse) in:
    - 234 patients (17.7%) with CD and 141 (24.9%) with UC/IC

Baseline exercise status was measured using the validated Godin leisure time activity index

- Conclusion:
  - A trend was observed that higher exercise level was associated with reduced likelihood of developing active disease (OR 0.87, 95% CI 0.67-1.12) after adjusting for age and global health

Stress in IBD Is Associated With Increased Symptoms, But Is Not Associated With Elevated Fecal Calprotectin

University of Manitoba IBD Research Registry

High perceived stress levels in both Crohn’s disease and ulcerative colitis were associated with increased clinical indices

- Crohn’s disease
  - HBI ≥ 5 (OR 2.03, 95% CI 1.04-3.98)
  - Active MIBDI (OR 2.48, 95% CI 1.30-4.74)

- Ulcerative colitis
  - PTI ≥ 5 (OR 2.33, 95% CI 1.09-5.01)
  - Active MIBDI (OR 2.68, 95% CI 1.22-5.59)

High perceived stress levels were not associated with elevated fecal calprotectin (>250ug/g)

- Crohn’s disease (OR 1.19, 95% CI 0.64-2.19)
- Ulcerative colitis (OR 0.76, 95% CI 0.35-1.66)


HBI, Harvey-Bradshaw Index; MIBDI, Manitoba IBD Index; PTI, Powell-Tuck Index.

Toxicity of medications

They almost never happen but good to be informed
Comparative toxicity of various therapies for Crohn’s disease

Mortality associated with current and recent corticosteroid use – adjusted HR (95% CI)

<table>
<thead>
<tr>
<th>Hazard Ratio</th>
<th>Current use of corticosteroids</th>
<th>Recent use of corticosteroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.81</td>
<td>95% CI: (2.26-3.5)</td>
<td></td>
</tr>
<tr>
<td>2.49</td>
<td>95% CI: (1.65-3.75)</td>
<td></td>
</tr>
</tbody>
</table>

Infections and mortality in the TREAT registry: 15,000 patient-years of experience

Multivariate analysis

Risk factors for opportunistic infections in IBD: A case-control study

100 cases of opportunistic infections

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 medication</td>
<td>2.7 (1.5–4.8)</td>
<td>0.0014</td>
</tr>
<tr>
<td>2 medications</td>
<td>9.7 (3.3–28.2)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>3 medications</td>
<td>Infinite</td>
<td>Overall P &lt; 0.0001</td>
</tr>
<tr>
<td>Steroids alone</td>
<td>2.2 (1.1–4.8)</td>
<td>0.037</td>
</tr>
<tr>
<td>6-MP/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>6-MP/AZA + steroids</td>
<td>15.7 (4.1–59.5)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>6-MP/AZA + IFX</td>
<td>1.6 (0.1–18.7)</td>
<td>0.71</td>
</tr>
<tr>
<td>6-MP/AZA + IFX + steroids</td>
<td>Infinite</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

6-MP = 6-mercaptopurine; AZA = azathioprine; IBD = inflammatory bowel disease; IFX = infliximab.

Anti-TNF Antibody Toxicity

- Immunogenicity (antibodies to infliximab, adalimumab, certolizumab pegol)
- Infusion reactions (infliximab)
- Delayed hypersensitivity reactions (infliximab)
- Injection-site reactions (adalimumab, certolizumab pegol)
- Autoantibody formation (predominantly infliximab, adalimumab)
- Drug-induced lupus (predominantly infliximab)
- Non-Hodgkin’s lymphoma
- Hepatosplenic T-cell lymphoma in children on anti-TNF + azathioprine
- Skin cancer
- ? Solid tumors
- Serious infections
- Opportunistic infections (including tuberculosis, histoplasmosis, coccidiomycosis)
- Demyelination

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

<table>
<thead>
<tr>
<th>Event</th>
<th>Frequency Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stop therapy due to adverse event</td>
<td>11%</td>
</tr>
<tr>
<td>Allergic reactions</td>
<td>2%</td>
</tr>
<tr>
<td>Nausea</td>
<td>2%</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>2%</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>3%</td>
</tr>
<tr>
<td>Serious infections</td>
<td>5%</td>
</tr>
<tr>
<td>non-Hodgkin’s lymphoma</td>
<td>0.04% (4/10,000)</td>
</tr>
</tbody>
</table>

Siegel CA, et al. APT 2005 (weighted average); Siegel CA, et al. CGH 2009
Methotrexate

Toxicity

- Rash
- Nausea, mucositis, diarrhea
- Bone marrow suppression
- Hypersensitivity pneumonitis
- Increased LFTs
- Hepatic fibrosis/cirrhosis

Lymphomas and infections
Epidemiology of NHL

- 1960s-1990s: NHL increased 2%-4% annually
  - 5th most common in US
  - 10th most common worldwide

Treatment and Risk for Lymphoma

- Causality bias (ie, incipient lymphoma present at time of initiating therapy)
  - 26 cases of lymphoma following treatment with etanercept or infliximab in postmarketing surveillance
  - 81% NHL vs 19% Hodgkin, multiple subtypes
  - Median interval between initiating therapy and lymphoma = 8 weeks
**Risk of Lymphoma Associated with Immunomodulators**

- **19,486 IBD patients**
  - 30.1% currently receiving thiopurines
  - 14.4% discontinued thiopurines
  - 55.5% never exposed to thiopurines

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Rate per 10,000 pt-years</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current use</td>
<td>9.0</td>
<td>5.0-14.9</td>
</tr>
<tr>
<td>Discontinued</td>
<td>2.0</td>
<td>0.2-7.2</td>
</tr>
<tr>
<td>Never exposed</td>
<td>2.6</td>
<td>1.0-5.7</td>
</tr>
</tbody>
</table>

Receiving thiopurines vs. never exposed

HR 5.28 (2.01-13.9)


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**Cesame Trial**

19,486 patients with IBD in a nationwide French cohort from 5/04-6/05

Multivariate Hazard Ratio for Lymphoproliferative Disorder From Thiopurine Use = 5.28 (2.01-13.9)

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)

<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

Risk of Lymphoma Returns to Normal After Stopping Thiopurines

- 36,891 VA patients with UC with a median follow up of 6.7 years and a median age of 60 years at inclusion
  - 4,734 patients using thiopurines; median duration of exposure: 0.97 years

- 142 confirmed lymphoma cases

<table>
<thead>
<tr>
<th>Thiopurine Use</th>
<th>Incidence Rate (per 1,000 person-years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unexposed</td>
<td>0.6</td>
</tr>
<tr>
<td>During</td>
<td>2.3</td>
</tr>
<tr>
<td>After stopping</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Risk of Developing NH Lymphoma

Patient receiving anti-TNF + Immunomodulator Therapy for 1 year

Risk without medication

Risk of Developing NH Lymphoma

Patient receiving anti-TNF + Immunomodulator Therapy for 1 year

Ten Thousand People
pictures to help you see your risks

Risk with IM monotherapy

Risk with combination therapy

Serious Infection and Lymphoma Risk With Anti-TNF Therapy for Pediatric IBD: Systematic Review

- **1,979 patients, more than 80% on concomitant immunomodulators**
- **Lymphoma rate of pediatric IBD patients exposed to anti-TNF agents: 2.3/10,000 patient-years of follow-up**

<table>
<thead>
<tr>
<th></th>
<th>Baseline incidence (per 10,000 PY)</th>
<th>SIR for anti-TNF, P value, (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphoma (general pediatric population)</td>
<td>0.58</td>
<td>3.88, P=0.15, (0.38-21.7)</td>
</tr>
<tr>
<td>Immunomodulators (pediatric use)</td>
<td>4.5</td>
<td>0.52, P=0.54, (0.04-7.1)</td>
</tr>
</tbody>
</table>

**Conclusion:**
- Risk of serious infection, lymphoma, and death with anti-TNF in pediatric IBD is very low, and much lower than in adults


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Serious Infection in Children Receiving IBD Therapies: A Multicenter, Prospective, Pediatric (The DEVELOP) Registry

- **4,343 patients enrolled; 2,586 were exposed to anti-TNF biologics, 2,503 received IFX and 1,757 received non-biologic therapies**
- **Identified patients (mean age= 13) within 90 days of anti-TNF exposure who experienced a serious infection**
- **Absolute rate of serious infections per 100 patient-years of follow-up**
  - Anti-TNF exposed = 5.82 versus 2.89 for anti-TNF unexposed (P<0.05)
  - Anti-TNF monotherapy = 3.51 versus 8.09 for anti-TNF + IM combination therapy
- **Factors associated with a higher risk of time to first serious infection include:**
  - Prior hospitalization within 1 year, age, infliximab use, immunomodulator use, higher physician global assessment
- **Conclusion:**
  - Pediatric patients receiving anti-TNF therapy have an increased risk of superficial infections, abdominal abscesses, and viral infections

Malignancies in Children Receiving IBD Therapies: A Multicenter, Prospective, Pediatric (The DEVELOP) Registry

"† Malignancy event rates from DEVELOP were compared with the expected event rates using the SEER database; adjusted for age, gender, and race

"‡ 4,343 patients enrolled
- 2,586 exposed to anti-TNFs (2,503 to IFX); 1,757 received non-biologic therapies

<table>
<thead>
<tr>
<th>Medication use</th>
<th>Observed Rate of Malignancies (per 10,000 patients)</th>
<th>Standardized Incidence Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-TNF + immunomodulator combination</td>
<td>10.7</td>
<td>5.73 (1.56-14.70)</td>
</tr>
<tr>
<td>Immunomodulator monotherapy</td>
<td>12.4</td>
<td>7.12 (1.47-20.80)</td>
</tr>
<tr>
<td>Anti-TNF monotherapy</td>
<td>0</td>
<td>0 (0-21.40)</td>
</tr>
<tr>
<td>Neither Anti-TNF nor immunomodulator</td>
<td>0</td>
<td>0 (0-17.90)</td>
</tr>
</tbody>
</table>


It is a subgroup of patients at higher risk for infections and lymphomas

- 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
Age ≥ 65 Is A Predictor of Infectious Complications in IBD Patients

** Retrospective cohort study of 292 patients, 146 patients ≥ 65 years

<table>
<thead>
<tr>
<th></th>
<th>Incidence Rate Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elderly IBD patients</td>
<td>1.58</td>
<td>1.14-2.18</td>
</tr>
<tr>
<td>Elderly IBD patients on corticosteroids</td>
<td>3.15</td>
<td>1.55-6.41</td>
</tr>
<tr>
<td>Elderly IBD patients on corticosteroids and immunomodulator therapy</td>
<td>10.58</td>
<td>1.27-87.91</td>
</tr>
<tr>
<td>Elderly IBD patients on corticosteroids and anti-TNF therapy</td>
<td>10.64</td>
<td>1.95-58.10</td>
</tr>
</tbody>
</table>

** Conclusions:
- Increasing age is associated with an increased risk for infection in IBD patients on corticosteroids, immunomodulators, and anti-TNF therapies
- Corticosteroids had the highest incidence rate ratio for infection as compared to all other therapies
- Infectious risk is increased when corticosteroids are added to an immunomodulator or to an anti-TNF


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** IBD, TNF-α Antagonists and Hepatosplenic T-Cell Lymphoma (HSTCL)

- Kotlyar et al (DDW Abstract S1133)
  - 24 cases of HSTCL in patients with IBD
  - Nearly all male
  - Nearly all dead
  - Nearly all <40 years old
  - 90% had ≥3 years of AZA/6-MP
  - 75% exposed to TNF-α antagonists

- HSTCL not reported in other autoimmune populations treated with TNF-α antagonists and purine analogs
### Female Gender and Pancolitis Are Associated With an Increased Risk of *Clostridium difficile* in UC

- **Aims:** identify genetic and clinical factors associated with *Clostridium difficile* (*C. diff*) in UC
- **Methods:** single-center registry, 2005-2012
- **Results:** 319 UC patients, 29 of which had *C. diff*
  - 8 known IBD genetic loci are associated with *C. diff*
  - Multivariate analysis revealed 4 clinical variables associated with *C. diff*:
    - Female gender (OR 3.07, 95% CI 1.26 – 7.52)
    - Pancolitis (OR 2.52, 95% CI 1.03 – 6.17)
    - Age >55 years (OR 0.21, 95% CI 0.05 – 0.90)
    - Anti-TNF use (OR 0.29, 95% CI 0.12 – 0.76)


### Thromboembolic Risk in Hospitalized IBD Patients

- **Single center study:**
  - 173 patients experienced 200 thromboembolic events over an 11-year period
  - DVT 48%; PE 12%; thrombophlebitis 12%; mesenteric venous thrombosis 4%; coronary ischemia 6%; stroke/TIA 5%

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Proportion of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery (IBD related / unrelated)</td>
<td>30% / 6%</td>
</tr>
<tr>
<td>Malignancy (past or current)</td>
<td>17%</td>
</tr>
<tr>
<td>Estrogen use</td>
<td>9%</td>
</tr>
<tr>
<td>Personal / family history of TE</td>
<td>20% / 25%</td>
</tr>
<tr>
<td>Smoking</td>
<td>11%</td>
</tr>
<tr>
<td>Prothrombotic state</td>
<td>12% (20 of 44 patients tested)</td>
</tr>
</tbody>
</table>

- **Identified Prothrombotic State**
  - Antiphospholipid Ab: 3 (7)
  - Factor VIII mutation: 3 (7)
  - Hyperhomocysteinemia: 3 (7)
  - Lupus anticoagulant: 9 (20)
  - Protein S deficiency: 2 (5)

- **Prophylaxis was documented in only 40% of inpatients prior to the diagnosis of the thromboembolic event**

Extensive Colitis Predicts Early Hospital Readmission in Patients With Severe Ulcerative Colitis

**Retrospective single center cohort study**
- 229 patients discharged following hospitalization for severe UC
  - 30-day readmission 11.7%
  - 90-day readmission 20.5%

**47% of early readmissions were for urgent colectomy**

<table>
<thead>
<tr>
<th>Predictors of 30-Day Readmission</th>
<th>Odds Ratio (OR) (95% CI)</th>
<th>Predictors of 90-Day Readmission</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extensive colitis</td>
<td>3.59 (1.41-9.13)</td>
<td>Extensive colitis</td>
<td>2.43 (1.21-4.89)</td>
<td>0.01</td>
</tr>
<tr>
<td>Albumin on first admission</td>
<td></td>
<td>Albumin on first admission</td>
<td>0.63 (0.38-1.00)</td>
<td>0.07</td>
</tr>
<tr>
<td>Being admitted to a housestaff service</td>
<td></td>
<td>Being admitted to a housestaff service</td>
<td>2.12 (1.09-4.11)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

**Rate of 90-day readmission by discharge medications:**
- Steroids only > cyclosporine or biologic monotherapy > combination cyclosporine or biologic plus immunomodulator


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Endoscopic Surveillance After Resection of Polypoid Dysplasia in Ulcerative Colitis Is Safe and Effective

**Meta-analysis** using MOOSE (Meta-analysis of Observational Studies in Epidemiology) criteria

**10 constituent published studies looking at nonsurgical management after resection of dysplastic polyps in ulcerative colitis**

**Pooled Case series and not randomized trials**

**Pooled results**
- Rate of CRC is **6.7** (3.5-12.9) per 1000 patient years
- Rate of CRC or high grade dysplasia is **9.0** (5.1-15.8) per 1000 patient years
- Rate of any dysplasia is **60** (48-71) per 1000 patient years

**Patients may continue with every 6 month surveillance provided that polyp(s) are completely resected**

Skin issues related to IBD

New psoriasis after anti-TNF therapy

- Hundreds of cases
- Appears in 50% within 6 months, but can occur up to several years after anti-TNF use
- Adalimumab (5X) > etanercept (4X) > infliximab (3X) increased risk
- Usually new onset but can worsen existing psoriasis
- Palmoplantar pustulosis (32%)
- Can be severe scalp involvement or genital

Palmoplantar psoriasis

Palmoplantar psoriasis

Palmoplantar psoriasis
Anti-TNF Antibody-Induced Psoriasiform Skin Lesions Respond to Ustekinumab

**21 patients with anti-TNF antibody-induced psoriasis prospectively recruited from 434 anti-TNF treated IBD patients; Genotyping for IL23R and IL12B variants performed**

**Results:**
- 19/331 CD – 5.7%, 2/103 UC patients – 1.3%
- Predictors of skin lesions using multivariate analysis:
  - Smoking (OR 4.24, 95% CI 1.55-13.6; P=0.007)
  - Increased BMI (OR 1.12, CI 1.01-1.24; P=0.029)
- 7/21 with severe skin lesions and/or alopecia treated with ustekinumab – 100% response

**Conclusions:**
- Anti-TNF antibody-induced psoriasiform skin lesions are not uncommon
- Smoking and increased BMI are predictors
- Ustekinumab can be used to successfully treat severe cases
- Dose effect in development of psoriasiform lesions were not analyzed, and no dose or frequency reduction was attempted
- Genetic factors predict severe cases – IL23R and IL12B variants


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IBD Is Associated With an Increased Risk of Melanoma Independent of Biologic Use

**Systematic review and meta-analysis: 12 studies (9 population based, 2 large administrative databases, 1 hospital-based)**
- 172,837 patients with IBD – 92,208 with CD and 79,360 with UC
- 118 cases of melanoma from 1940-2009

<table>
<thead>
<tr>
<th>Sub-groups</th>
<th>Categories</th>
<th>No. of studies</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of IBD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Crohn's Disease</td>
<td>7</td>
<td>1.51</td>
<td>1.14-1.98</td>
</tr>
<tr>
<td></td>
<td>Ulcerative Colitis</td>
<td>7</td>
<td>1.23</td>
<td>1.01-1.50</td>
</tr>
<tr>
<td>Biologic era (1998 onwards)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pre-biologic</td>
<td>8</td>
<td>1.52</td>
<td>1.02-2.25</td>
</tr>
<tr>
<td></td>
<td>Biologic era</td>
<td>2</td>
<td>1.08</td>
<td>0.59-1.96</td>
</tr>
<tr>
<td></td>
<td>Across both eras</td>
<td>2</td>
<td>1.56</td>
<td>0.86-2.84</td>
</tr>
</tbody>
</table>

**Crude incidence rate of melanoma 27.5 / 100,000 person-years**

**Relative risk (RR) of melanoma in IBD: 1.43 (95% CI 1.08 – 1.88)**
- No increased risk with thiopurines (RR 1.10, 95% CI 0.71-1.36) or biologics (RR 1.08, 95% CI 0.59-1.96)

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 (IMs), anti–tumor necrosis factor (anti-TNF) agents
  - Timing in relationship to a disease complication
- Model concordance index (Harrell’s C = 0.81)

Siegel CA et al. Inflamm Bowel Dis. 2011;17:30.

Control Panel and Output

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

Siegel CA et al. Inflamm Bowel Dis. 2011;17:30.
Maintaining Remission on Antimetabolites After Stopping Infliximab in Crohn’s Disease: A Prospective Cohort Study

Kaplan-Meier Curve of Relapse

- n=52 relapses/115 patients
- Median follow-up 28+/- 2 months
- Median time to relapse: 16.4 months

Predictive Model for Time-to-Relapse

Kaplan Meier time-to-relapse curves according to multivariate models and scores generated through Cox model using multiple imputations method

Deleterious factors were:
- No previous surgery
- Steroid use within 12-6 months before infliximab withdrawal
- Male gender
- Haemoglobin ≤14.5 g/dl
- Leukocyte count >6×10⁹/l
- hsCRP ≥5 mg/l
- Fecal calprotectin ≥230 µg/g
- CDEIS >0
- Infliximab trough ≥2 mg/l
What should doctors do to minimize risk

- Routine laboratory monitoring
- Age and risk: older men and younger men and thiopurines
- Vaccinate patients:
  - Seasonal flu
  - HPV (young women)
  - Pneumococcal vaccine
- Avoid live vaccines if already on immunomodulators:
  - Varicella
  - MMR
- Skin exams yearly
- Develop a simple checklist