IBD AND CANCER

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DISCLOSURES

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Speakers bureau:
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BACKGROUND

• IBD is an intriguing model among chronic inflammatory disorders

• Chronic inflammation, specific life style (i.e. smoking) and systemic immune dysregulation lead to impairment of immune surveillance

• Immunosuppressants (IMS) may reduce the incidence of inflammation-related cancers but also promotes IMS-related cancers
OBJECTIVES

☑ Review the cancer risk related to IBD therapy

☑ Understand the difference among and implication of absolute and relative risk

☑ Strategies for risk minimization
DRUG RELATED CANCER IN IBD

IS CUMULATIVE CANCER RISK MORE ELEVATED IN IBD FOR?

• Use of Thiopurines
• Use of anti-TNF agents
• Use of combo therapy (Thiopurines + anti-TNF)
• Chronically active extensive disease
BACKGROUND RISK OF CANCER IN IBD

INCIDENCE/100,000 patients/year

- NMSC: 90 x 10
- Colorectal: 80
- Melanoma: 50
- Small bowel: 50
- Lymphoma: 20
- Intestinal Lymp: 10
- CholangioCr: 8
- Anal cancer: 1.5
- Leukemia: 1.5

6 Annese V et al. European Evidence-Based Consensus: IBD ad Malignancies. JCC 2015;945-65
IBD THERAPY AND CANCER RISK

• 5-Aminosalicylates
• Corticosteroids
• Thiopurines
• Methotrexate
• Calcineurin inhibitors
• Anti-TNF
• Vedolizumab, Ustekinumab
5-AMINOSALYCYLATES

No increased cancer risk in IBD!

Further, high-quality prospective research is warranted to evaluate the potential chemoprevention role.

Last systematic review and meta-analysis = 31 studies, 2137 case of colorectal neoplasia, moderate heterogeneity.

Exposure to 5-aminosalicylates was protective against cancer (RR = 0.58, 95% CI: 0.45-0.74) and dysplasia (RR = 0.54, 95% CI: 0.35-0.84), in either cohort, case-control and population-based studies.

The effect of sulfasalazine was marginally nonsignificant (RR = 0.72, 95% CI: 0.51-1.01).

Bonovas S et al. Alim Pharm & Ther 2017;45:1179-92
CORTICOSTEROIDS

No increased cancer risk in IBD!
Patients with IBD treated with thiopurines are at increased risk of cancer [EL3]

Thiopurine cytotoxicity is mediated by the incorporation of 6-thioguanine instead of guanine during DNA replication. The error stimulates the mismatch repair system but repair may be incomplete. 

Carcinogenetic mechanisms:
- Mutations of cell DNA (i.e. skin)
- Impaired immuno-surveillance
- Reduced number and function of immune cells
- Facilitate proliferation with microsatellite instability

10 Annese V et al. European Evidence-Based Consensus: IBD ad Malignancies. JCC 2015;945-65
THIOPURINES AND HAEMATOLOGICAL MALIGNANCIES

In IBD patients treated with thiopurines, there is an excess risk of lymphoma [EL1]

**SIR = 5.7** (95% CI 3.2 – 10.1) IBD under therapy
No excess risk in former user
Absolute risk x 2-3 men vs women
Highest *absolute risk* patients over 50 yrs (**2.6/1000 pts/yr**)
Lowest *absolute risk* in middle age (**0.3-0.9/1000 pts/yr**)

The SIR does not appear to increase substantially beyond the first year of treatment
Figure: Incidence rates of lymphoproliferative disorders according to thiopurine exposure grouped by age at entry in the cohort
LD=lymphoproliferative disorder.

12 Beaumerie L et al Lancet, 2009 374 1617-25
IBD patients who are receiving thiopurines are at increased risk for Non Melanoma Skin Cancer (NMSC) [EL3]; it is not clear whether the excess risk persists after thiopurine withdrawal. Does not seem increased the risk of melanoma [EL3]

The carcinogenic effect has been attributed to:
- increase UVA-induced DNA damage
- increased production of reactive oxygen species in skin
- possible direct induction of mutations of PTCH gene

There is a predominant occurrence of squamous-cell carcinoma in spite of basal-cell carcinoma (more common in general population)

Meta-analysis pool adjusted HR in IBD = 2.3 (95% CI: 1.50 to 3.45)

No persistent risk after withdrawal
Nested case-control study of Manitoba population – Singh H et al Gastro 2011;141:1612

14 Peyrin-Biroulet L et al Gastroenterology 2011;141:1621–1628
THIOPURINES AND URINARY TRACT CANCERS

In the CESAME observational cohort, ten and six patients developed respectively kidney and bladder cancers.

The SIR was 3.4 (95% CI 1.47-6.71, P=0.006) with an incidence ratio of 0.48/1000 pt/yr

The multivariate-adjusted HR = 2.8 (95% CI 1.04-7.68, P=0.04) of patients receiving thiopurines vs not receiving

Other significant factors were male gender (HR=4) and increasing age (HR over 65 years = 13.2)
METHOTREXATE

No studies specifically focused on cancer risks in IBD (few patients treated)

Many studies in rheumatoid arthritis all negative, but possibly underpowered

Among 9460 individuals (6841 with RA and 2788 with IBD), the incidence rate of a second NMSC increased with 1 year or more of methotrexate use (HR, 1.24; 95% CI, 1.04-1.48).

CALCINEURIN INHIBITORS

In the post-transplant state **excess risk for NHL**
They occurred earlier than those related to thiopurines, are more likely to involve the lymph nodes and small intestine, and regress more frequently after reduction of immunosuppression.

No data area available in IBD patients; in general not prolonged use
ANTI-TNF

Tumor necrosis factor alpha is a cytokine produced by activated T cells and macrophages, which exerts necrotizing effects on tumor cells in vitro.

Inhibition of TNF-alpha has therefore been hypothesized to increase the overall cancer risk.

There is currently no evidence the overall excess risk of cancer and lymphoma is increased in IBD patients treated with anti-TNF agents alone [EL4]

<table>
<thead>
<tr>
<th>Biologic placebo</th>
<th>OR (95% CI)</th>
<th>Weight (fixed)</th>
<th>Weight (random)</th>
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</thead>
<tbody>
<tr>
<td><strong>Adalimumab versus placebo</strong></td>
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<tr>
<td>Suzuki et al., 2014</td>
<td>4.12 (0.12, 141.05)</td>
<td>1.5%</td>
<td>2.7%</td>
</tr>
<tr>
<td>Watanebe et al., 2012 (induction)</td>
<td>2.38 (0.04, 156.17)</td>
<td>1.2%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Sandborn et al., 2012 (ULTRA 2)</td>
<td>5.06 (0.24, 105.31)</td>
<td>1.6%</td>
<td>3.5%</td>
</tr>
<tr>
<td>Rainsch et al., 2011 (ULTRA 1)</td>
<td>0.16 (0.01, 2.67)</td>
<td>0.6%</td>
<td>4.3%</td>
</tr>
<tr>
<td>Sandborn et al., 2007 (CLASSIC-II)</td>
<td>0.23 (0.01, 4.63)</td>
<td>5.7%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Colombel et al., 2007 (CHARM)</td>
<td>0.25 (0.01, 4.76)</td>
<td>5.8%</td>
<td>3.0%</td>
</tr>
<tr>
<td>Fixed effect model</td>
<td>0.34 (0.26, 0.46)</td>
<td>25.3%</td>
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</tr>
<tr>
<td>Random effects model</td>
<td>0.70 (0.19, 2.56)</td>
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<td>20.2%</td>
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<tr>
<td><strong>Cetuximab pegol versus placebo</strong></td>
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<tr>
<td>Sandborn et al., 2011</td>
<td>2.98 (0.12, 74.60)</td>
<td>1.0%</td>
<td>3.0%</td>
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<tr>
<td>Sandborn et al., 2007 (PRECISE 1)</td>
<td>0.99 (0.14, 7.10)</td>
<td>6.5%</td>
<td>8.7%</td>
</tr>
<tr>
<td>Fixed effect model</td>
<td>1.39 (0.27, 7.09)</td>
<td>8.1%</td>
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</tr>
<tr>
<td>Random effects model</td>
<td>1.34 (0.25, 7.17)</td>
<td>--</td>
<td>11.9%</td>
</tr>
<tr>
<td><strong>Golimumab versus placebo</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Rutgeerts et al., 2016 (PURSUIT-IV)</td>
<td>2.37 (0.04, 142.87)</td>
<td>1.3%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Sandborn et al., 2014 (PURSUIT-MI)</td>
<td>2.51 (0.05, 102.84)</td>
<td>1.4%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Sandborn et al., 2014 (PURSUIT-SC)</td>
<td>0.46 (0.03, 7.22)</td>
<td>4.5%</td>
<td>4.4%</td>
</tr>
<tr>
<td>Fixed effect model</td>
<td>1.20 (0.20, 7.39)</td>
<td>7.2%</td>
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<tr>
<td>Random effects model</td>
<td>1.06 (0.15, 7.46)</td>
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<td>8.8%</td>
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<tr>
<td><strong>Infliximab versus placebo</strong></td>
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<tr>
<td>Colombel et al., 2010 (SONIC)</td>
<td>0.20 (0.01, 4.17)</td>
<td>8.1%</td>
<td>3.0%</td>
</tr>
<tr>
<td>Rutgeerts et al., 2006 (ACT 1)</td>
<td>1.03 (0.11, 146.17)</td>
<td>1.4%</td>
<td>2.6%</td>
</tr>
<tr>
<td>Rutgeerts et al., 2005 (ACT 2)</td>
<td>0.51 (0.03, 7.6)</td>
<td>4.3%</td>
<td>4.4%</td>
</tr>
<tr>
<td>Hansen et al., 2002 (ACCENT I)</td>
<td>0.58 (0.18, 5.58)</td>
<td>8.7%</td>
<td>11.5%</td>
</tr>
<tr>
<td>Rutgeerts et al., 1999</td>
<td>0.32 (0.01, 6.03)</td>
<td>4.9%</td>
<td>3.2%</td>
</tr>
<tr>
<td>Regueiro et al., 2018 (PREVENT)</td>
<td>0.58 (0.11, 4.10)</td>
<td>9.5%</td>
<td>10.3%</td>
</tr>
<tr>
<td>Fixed effect model</td>
<td>0.71 (0.29, 1.72)</td>
<td>36.6%</td>
<td>--</td>
</tr>
<tr>
<td>Random effects model</td>
<td>0.59 (0.26, 1.39)</td>
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<td>35.7%</td>
</tr>
<tr>
<td><strong>Natalizumab versus placebo</strong></td>
<td></td>
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</tr>
<tr>
<td>Targan et al., 2007 (ENCORE)</td>
<td>4.36 (0.23, 106.09)</td>
<td>1.6%</td>
<td>3.0%</td>
</tr>
<tr>
<td>Sandborn et al., 2005 (ENACT-2)</td>
<td>1.00 (0.68, 1.69)</td>
<td>3.2%</td>
<td>4.4%</td>
</tr>
<tr>
<td>Fixed effect model</td>
<td>2.32 (0.34, 15.85)</td>
<td>4.8%</td>
<td>--</td>
</tr>
<tr>
<td>Random effects model</td>
<td>2.06 (0.26, 16.13)</td>
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<td>7.9%</td>
</tr>
<tr>
<td><strong>Vedolizumab versus placebo</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Sands et al., 2014 (GEMINI 3)</td>
<td>3.00 (0.12, 74.67)</td>
<td>1.6%</td>
<td>3.3%</td>
</tr>
<tr>
<td>Sandborn et al., 2013 (GEMINI 2 maintenance)</td>
<td>2.50 (0.07, 104.43)</td>
<td>1.4%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Faugeron et al., 2013 (GEMINI 1, maintenance)</td>
<td>0.25 (0.02, 2.61)</td>
<td>8.6%</td>
<td>5.8%</td>
</tr>
<tr>
<td>Panacci et al., 2012</td>
<td>0.14 (0.01, 2.66)</td>
<td>6.1%</td>
<td>3.9%</td>
</tr>
<tr>
<td>Fixed effect model</td>
<td>0.65 (0.18, 2.36)</td>
<td>17.8%</td>
<td>--</td>
</tr>
<tr>
<td>Random effects model</td>
<td>0.53 (0.12, 2.32)</td>
<td>--</td>
<td>15.4%</td>
</tr>
<tr>
<td>Fixed effect model</td>
<td>0.30 (0.14, 0.69)</td>
<td>100%</td>
<td>--</td>
</tr>
<tr>
<td>Random effects model</td>
<td>0.81 (0.06, 14.15)</td>
<td>100%</td>
<td>--</td>
</tr>
</tbody>
</table>

Figure 5. Forest plot for malignancies: results from individual studies and meta-analysis.

189,289 IBD patients included followed up for a median of 6.7 years; 50,405 were exposed to thiopurine monotherapy, 30,294 to anti-TNF monotherapy, and 14,229 to combination therapy, and 123,069 were never exposed during follow-up. In a multivariable Cox model, compared with unexposed patients, the risk of lymphoma was higher among those exposed to

**Thiopurine monotherapy** (adjusted hazard ratio [aHR], 2.60; 95% CI, 1.96-3.44; *P* < .001),

**Anti-TNF monotherapy** (aHR, 2.41; 95% CI, 1.60-3.64; *P* < .001),

or **combination therapy** (aHR, 6.11; 95% CI, 3.46-10.8; *P* < .001).

The risk was higher in patients exposed to combination therapy vs those exposed to thiopurine monotherapy (aHR, 2.35; 95% CI, 1.31-4.22; *P* < .001) or anti-TNF monotherapy (aHR, 2.53; 95% CI, 1.35-4.77; *P* < .001).

Lemaître M et al. JAMA 2017; 318(17): 1679–1686. Association Between Use of Thiopurines or Tumor Necrosis Factor Antagonists Alone or in Combination and Risk of Lymphoma in Patients With Inflammatory Bowel Disease
In patients with IBD treated with anti-TNF, the risk of cutaneous malignant melanoma is increased 1.3 fold [EL2].

Conditional Logistic regression – data expressed as OR

<table>
<thead>
<tr>
<th>Medicationa</th>
<th>Melanoma</th>
<th>NMSC</th>
<th>Melanoma</th>
<th>NMSC</th>
<th>Melanoma</th>
<th>NMSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any use</td>
<td>1.06 (0.77–1.45)</td>
<td>0.99 (0.92–1.08)</td>
<td>0.98 (0.63–1.53)</td>
<td>1.01 (0.90–1.13)</td>
<td>1.22 (0.76–1.96)</td>
<td>0.99 (0.89–1.11)</td>
</tr>
<tr>
<td>5-ASA</td>
<td>1.14 (0.95–1.36)</td>
<td>1.10 (0.72–1.67)</td>
<td>1.16 (0.95–1.41)</td>
<td>1.73 (0.53–5.63)</td>
<td>1.06 (0.69–1.64)</td>
<td></td>
</tr>
<tr>
<td>Biologic</td>
<td>1.94 (1.03–3.68)</td>
<td>1.85 (1.66–2.05)</td>
<td>1.99 (1.73–2.27)</td>
<td>1.31 (0.66–2.60)</td>
<td>1.63 (1.36–1.94)</td>
<td></td>
</tr>
<tr>
<td>Thiopurine</td>
<td>1.56 (1.05–2.32)</td>
<td>1.53 (1.04–2.26)</td>
<td>1.76 (1.24–2.50)</td>
<td>1.28 (0.79–2.09)</td>
<td>1.50 (1.02–2.19)</td>
<td></td>
</tr>
</tbody>
</table>

Retrospective cohort and nested case-control studies using administrative data from 1997-2009 (108,579 pts)

21 Long MD et al. Gastroenterology 2012:143:390--9
THE DILEMMA OF COMBO THERAPY

HEPATOSPLENIC T CELL LYMPHOMA

Reports to FDA AERS among patients with IBD
Thiopurine alone = 17
Anti-TNF alone = 1
Combination therapy = 23

Characteristics
Median age 22.5 (1 – 58)
93% male
Median time since initiation of thiopurines ≈ 6 years

A PRAGMATIC APPROACH

Consider this: Young males → induce with our “best” therapy (thiopurine+anti-TNF) and stop thiopurine (or anti-TNF) after 6-12 months when in deep remission.
VEDOLIZUMAB, USTEKINUMAB AND CANCER RISK

Data limited for Vedolizumab (six RCTs)
18 pts exposed (less 1%) had a malignancy in total 4811 PYs

Meta-analysis (6 Vedo + 2 Etro trials) \(RR = 0.78; \) 95% CI 0.15-4.02

PSOLAR Registry of Ustekinumab
12,093 patients (40,388 PY)
incidence rates were 0.68/100PY for malignancy, not significantly increased compared to other treatments

FDA Full Prescribing information 2016
No excess rate of malignancies except for NMSC

Papp K et al. J Drugs Dermatol 2015;14:706-14
ABSOLUTE vs RELATIVE RISK

MELANOMA
Absolute Risk in IBD ≈50/100,000/year
Relative Risk with anti-TNF x 2

LYMPHOMA
Absolute Risk in IBD 20/100,000/year
Relative Risk with Thiopurines x 2-3
Relative risk with anti-TNF x 2 (?)
Relative Risk with COMBO x 8

NMSC
Absolute Risk in IBD 900/100,000/year
Relative Risk with Thiopurines x 2

25 Annese V et al. European Evidence-Based Consensus: IBD ad Malignancies. JCC 2015;945-65
RISK MINIMIZATION STRATEGIES

- Tailor IMS therapy (mono, combo, duration) on the basis of risk factors, behavior, and natural history
- Retrieve a complete family history for cancer
- Perform adequate oncologic pre-screening (according to local guideline) and regular follow-up
- Consider the risk of being young male HBV negative
- Consider the increased risk while aging
Cancers caused by immunosuppressant therapy represent the minority of incident cancers observed in IBD patients.

Uncontrolled inflammation is an overwhelming risk factor.

Alternatives to thiopurines should be considered in young IBD male HBV-negative.

As soon as IBD is diagnosed patients should be instructed on the life long use of sun protection and regular skin examination.