Increased risk of morbidity associated with immunomodulatory therapy

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Immunomodulators in IBD

- Earlier
- Longer
- Higher doses
- Associated with other drugs
Immunomodulators safety data

- Clinical trials
- Case reports
- Case series
Experience in RCTs for Crohn’s disease generally favorable

Pooled odds ratio of study withdrawal due to AZA/6MP adverse events was 5.3 (95% CI, 2.2-12.6)

Withdrawals due to adverse events ranged from 0% to 15%
  - Average rate was 9% (vs. 2% in placebo)

“Real World” Experiences With AZA/6MP in 2002 - 4

<table>
<thead>
<tr>
<th>Setting</th>
<th>N</th>
<th>% Withdrawal Due to AE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olmsted Co, MN</td>
<td>102</td>
<td>25%</td>
</tr>
<tr>
<td>Canterbury, NZ</td>
<td>216</td>
<td>26%</td>
</tr>
<tr>
<td>Oxford, UK</td>
<td>622</td>
<td>28%</td>
</tr>
<tr>
<td>Groningen, NL</td>
<td>318</td>
<td>23%</td>
</tr>
<tr>
<td>Nijmegen, NL</td>
<td>50</td>
<td>22%</td>
</tr>
</tbody>
</table>

# Immunomodulator toxicity

<table>
<thead>
<tr>
<th>Azathiorine/6-MP</th>
<th>Methotrexate</th>
<th>Ciclosporin</th>
</tr>
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<td>Pancreatitis</td>
<td>Fatigue, malaise</td>
<td>Nausea, vomiting</td>
</tr>
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<td>Fever, rash, malaise</td>
<td>Headaches, dizziness</td>
<td>Headache, paresthesias</td>
</tr>
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<td>Digestive intolerance</td>
<td>“Post-injection” syndrome</td>
<td>Hypertrichosis</td>
</tr>
<tr>
<td>Bone marrow depression</td>
<td>Stomatitis</td>
<td>Hypertension</td>
</tr>
<tr>
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<td>Bone marrow depression</td>
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</tr>
<tr>
<td>Hepatotoxicity</td>
<td>HS pneumonitis</td>
<td>Seizure</td>
</tr>
<tr>
<td>Malignant neoplasm</td>
<td>Infections</td>
<td>Renal insufficiency</td>
</tr>
<tr>
<td>Lymphomas</td>
<td>Hepatotoxicity</td>
<td>Infections</td>
</tr>
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</tbody>
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### Immunomodulator toxicity

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<td>Infections</td>
</tr>
<tr>
<td></td>
<td>Lymphomas</td>
<td>Hepatotoxicity</td>
</tr>
</tbody>
</table>
Infections associated with immunomodulator therapy in IBD

Herpes simplex
CMV
Varicella zoster
EBV
HPV

M. Tuberculosis
M. Avium sp.
M. Xenopi
Listeria monocytogenes
Staphylococcus sp.
Nocardia
E. Coli
Salmonella sp.

Histoplasmosis
Aspergillus spp.
Cryptococcus spp.
Candida spp.
Coccidioides immitis
Blastomyces

Pneumocystis jiroveci
Toxoplasma gondii
Infections are a cause of death in IBD

- Population-based study of mortality and cause of death in CD:
  - Standardized mortality ratio for infections:
    - 8.33 (1.01-30.9) in women
    - 2.1 (0.03-11.8) in men

- Population-based study of mortality and cause of death in UC:
  - Standardized mortality ratio for infections:
    - 3.26 (0.6-9.5) in women
    - 1.6 (0.33-4.7) in men

- Infections were one of the two major contributors of UC-associated deaths (7.3%)

Long-term outcome of patients treated with IV ciclosporin for severe UC

- **Aspergillus pneumonia**
  60 yr old man, IVCS, AZA, ciclo
- **Aspergillus pneumonia**
  57 yr old man, IVCS, ciclo, surgery
- **Pneumocystis jiroveci**
  32 yr old man, CS, ciclo, AZA

TABLE 3. Adverse Reactions Occurring During CSA Therapy

<table>
<thead>
<tr>
<th>Condition</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
<td>16</td>
<td>18.6%</td>
</tr>
<tr>
<td>Tremor/paresthesia</td>
<td>8</td>
<td>9.3%</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>6</td>
<td>7.0%</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>5</td>
<td>5.8%</td>
</tr>
<tr>
<td>Hypertrichosis</td>
<td>5</td>
<td>5.8%</td>
</tr>
<tr>
<td>Gingival hyperplasia</td>
<td>5</td>
<td>5.8%</td>
</tr>
<tr>
<td>Headache</td>
<td>3</td>
<td>3.5%</td>
</tr>
<tr>
<td>Mortality (infections)</td>
<td>3</td>
<td>3.5%</td>
</tr>
<tr>
<td>Elevated liver tests (&gt;2×)</td>
<td>2</td>
<td>2.4%</td>
</tr>
<tr>
<td>Anaphylaxis (cardiac arrest)</td>
<td>1</td>
<td>1.2%</td>
</tr>
<tr>
<td>Seizure</td>
<td>0</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

Arts J et al. Inflamm Bowel Dis 2004
Factors that may predispose to infections in IBD patients on immunomodulators

- Severity of the disease
- Age
- Malnutrition
- Surgery
- Leucopenia
- Concomittant use of other medications
TREAT Registry: (Crohn’s Therapy Resource, Evaluation and Assessment Tool)

- >6000-patient Crohn’s disease (CD) registry primarily designed to assess long-term safety of infliximab in CD
- “Real world” experience—80% community, 20% academic
- Treatment at the discretion of the patient’s physician
- Patients to be followed for at least 5 years

### TREAT Registry—Serious Infections
#### Logistic Regression Data (Multivariate)

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current use of infliximab</td>
<td>0.979</td>
<td>0.619–1.547</td>
</tr>
<tr>
<td>Current use of 6MP/AZA/MTX</td>
<td>0.780</td>
<td>0.507–1.198</td>
</tr>
<tr>
<td>Current use of corticosteroids</td>
<td>2.278</td>
<td>1.478–3.511*</td>
</tr>
<tr>
<td>Current use of narcotic analgesics</td>
<td>2.412</td>
<td>1.560–3.730*</td>
</tr>
</tbody>
</table>

* P<0.001

Combination Therapy: Does It Synergistically Increase Infection Risk?

- 217 IBD patients from Stockholm treated with infliximab
  - 18 severe infections (8%)
  - 2 sepsis deaths (2 on GCS, none on AZA/6MP)

- 500 Crohn’s patients from Mayo treated with infliximab
  - 41 infections (8%)
  - 2 sepsis deaths, 2 pneumonia deaths (3 on GCS, none on AZA/6MP)

## Immunomodulators and postoperative septic complications

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th></th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>270 patients with Crohn’s disease</strong></td>
<td></td>
<td></td>
<td><strong>159 patients with IBD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroids &gt; 40mg</td>
<td>1.6</td>
<td>0.7-3.3</td>
<td>Steroids</td>
<td>3.7</td>
<td>1.2-10.9</td>
</tr>
<tr>
<td>6MP/AZA/MTX</td>
<td>1.1</td>
<td>0.6-2</td>
<td>6MP/AZA</td>
<td>1.7</td>
<td>0.6-4.3</td>
</tr>
<tr>
<td>Infliximab</td>
<td>1.0</td>
<td>0.5-2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Colombel JF et al. Am J Gastroenterol 2004

Aberra F et al. Gastroenterology 2003
IBD and infections

Is steroids the only bad guy?
Risk factors for opportunistic infections in IBD
A case-control study (n = 100; 1998-2003)

<table>
<thead>
<tr>
<th>Any Medication (5-ASA, AZA/6MP, Steroids, MTX, IFX)</th>
<th>Odds Ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Medication (5-ASA, AZA/6MP, Steroids, MTX, IFX)</td>
<td>3.5 (1.98-6.08)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>5-ASA</td>
<td>0.98 (0.61-1.56)</td>
<td>0.94</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>3.35 (1.82-6.16)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>6MP/AZA</td>
<td>3.07 (1.72-5.48)</td>
<td>0.0001*</td>
</tr>
<tr>
<td>MTX</td>
<td>4.0 (0.36-4.11)</td>
<td>0.26</td>
</tr>
<tr>
<td>IFX</td>
<td>4.43 (1.15-17.09)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Toruner M et al. DDW 2006
Risk factors for opportunistic infections in IBD
– A case-control study –

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td># medication (1)</td>
<td>2.65 (1.45-4.82)</td>
<td>0.0014</td>
</tr>
<tr>
<td># medication (2)</td>
<td>9.66 (3.31-28.19)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td># of medication (3)</td>
<td>Infinite</td>
<td></td>
</tr>
</tbody>
</table>

Toruner M et al. DDW 2006
### Risk factors for opportunistic infections in IBD

– A case-control study –

Actual Opportunistic Infections in IBD

<table>
<thead>
<tr>
<th></th>
<th>CMV</th>
<th>Candida</th>
<th>HSV</th>
<th>HZV</th>
<th>EBV</th>
<th>Histo</th>
<th>Blasto</th>
<th>Strep.</th>
<th>Myco.</th>
<th>HSV HZV</th>
<th>HZV Pelvic Abscess</th>
<th>E.Coli Candida</th>
<th>Crypto</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>3</td>
<td>7</td>
<td>7</td>
<td>16</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>IFX only</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td></td>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6MP-AZA only</td>
<td>4</td>
<td>1</td>
<td>5</td>
<td>5</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroids only</td>
<td></td>
<td>10</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IFX – 6MP/AZA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroids - 6MP/AZA</td>
<td>4</td>
<td>6</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Three</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

Toruner M et al. DDW 2006
Azathioprine and viral infections: a prospective study

230 consecutive patients receiving or not AZA, one year follow-up

Herpes bursts

Number of bursts/patient year

Aza+
N = 169

1,0

Aza-
N = 61

0,2

P = 0,04

Immunomodulators and the liver
Hepatotoxicity of methotrexate

32 IBD patients
MTX > 1500 mg

20 patients – liver biopsies

19 patients had mild histologic abnormalities,

1 patient had fibrosis,

Abnormal LFT found in 6 patients, but did not identify the patient with fibrosis

• Mean MTX dose: 2633 mg (range, 1500–5410 mg),
• given in a mean weekly dose of 20 mg (range, 5–25 mg)
• for a mean duration of 131.7 wk (range, 66–281 wk).

Conclusion: surveillance liver biopsy based on cumulative MTX dose not required in IBD, except for patients with other risk factors

Te H et al. Am J Gastroenterol 2000
AZA/6MP Hepatotoxicity

- Overall prevalence of biochemical abnormalities: 3-4%
- Most of these are dose-dependent
  - Related to over-accumulation of 6MMP due to high TPMT? Controversial
  - May resolve spontaneously or with dose reduction
- Rare occurrence of veno-occlusive disease and nodular regenerative hyperplasia

Dubinsky M. Clin Gastroenterol Hepatol 2004
Thiopurine metabolism – a simplified scheme

Methylated metabolites

AZA 6-MP

MMP

TPMT

TPMT

MeTIMP

Purine synthesis

Phosphorylated metabolites

TGN

6TG

TPMT

HGPRT

ITPase

IMPDH

6-TU

6-TITP

6-TMP

XO
Hepatotoxicity of 6-thioguanine therapy

111 IBD patients receiving 6TG therapy

29/111 (26.1%) abnormal liver chemistry and/or evidence of hematologic toxicity attributable to 6-TG therapy

17/29 underwent liver biopsy

13/17 (76%) NRH by reticulin silver impregnation method

9/82 patients without abnormal LFT elected to undergo liver biopsy

5/9 (55%) specimens showed abnormal liver histology
  • 3/9 NRH
  • 2/9 early periportal fibrosis

Dubinsky M et al. Gastroenterology 2003
Nodular regenerative hyperplasia with portal hypertension in patients with inflammatory bowel disease treated with azathioprine

- Retrospective review of cases registered in 11 medical centers
- 36 cases of NRH (29 M, 7 F) were identified between 1994 and 2005
- The median time between the start of AZA and diagnosis of NRH was 48.5 mos (6-187).
- The median dose of AZA was 2 mg/kg/d (1.5-3).
- NRH was suspected on clinical and/or morphological evidence of portal hypertension (PHTN) in 16
- 14 developed severe complications of PHTN with variceal haemorrhage in 9.

Vernier-Massouille G, DDWW 2006
Immunomodulators, lymphomas and cancers
Baseline Risk of Lymphoma in IBD

- Studies from referral centers indicate a twofold to sixfold increase in risk
  - Referral bias?
  - Risk increases with increased severity?
- Population-based studies indicate little or no increased risk, with few exceptions
# Lymphoma Risk in IBD Patients on AZA/6MP Meta-Analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
<th>N</th>
<th>Obs</th>
<th>Exp</th>
<th>SIR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kinlen</td>
<td>U.K.</td>
<td>321</td>
<td>2</td>
<td>0.16</td>
<td>12.5 (1.2 - 46)</td>
</tr>
<tr>
<td>Connell</td>
<td>London</td>
<td>755</td>
<td>0</td>
<td>0.52</td>
<td></td>
</tr>
<tr>
<td>Farrell</td>
<td>Dublin</td>
<td>238</td>
<td>2</td>
<td>0.05</td>
<td>37.5 (3.5 - 138)</td>
</tr>
<tr>
<td>Fraser</td>
<td>Oxford</td>
<td>626</td>
<td>3</td>
<td>0.65</td>
<td>4.6 (0.9 - 13.7)</td>
</tr>
<tr>
<td>Korelitz</td>
<td>New York</td>
<td>486</td>
<td>3</td>
<td>0.61</td>
<td>4.9 (0.9 - 14.5)</td>
</tr>
<tr>
<td>*<em>Lewis</em></td>
<td>GPRD</td>
<td>1465</td>
<td>1</td>
<td>0.64</td>
<td>1.6 (0.001 - 9)</td>
</tr>
<tr>
<td><strong>Pooled</strong></td>
<td></td>
<td>3891</td>
<td>11</td>
<td>2.63</td>
<td>4.2 (2.1 - 7.5)</td>
</tr>
</tbody>
</table>

Sensitivity analyses: when papers with highest or lowest SIRs were excluded, results remained significant (range, 3.5 - 5.2)

* : population-based study

Kandiel et al, Gut 2005

« The increased risk of lymphoma could be a result of the medication, the severity of the underlying disease or a combination of the two »
Inflammatory chronic disease and excess risk of NHL

- Due to chronic inflammation
  - Established in Sjögren syndrome \(^1\):
  - Frequent extranodal and marginal zone-type NHL
  - Usually not EBV-associated
  - Role of chronic autoantigenic stimulation ?

- Due to immunosuppression
  - EBV-associated in most cases
  - Spontaneous regression in some cases (one in CD \(^2\))

\(^1\) Royer et al., Blood 1997
\(^2\) Larvol et al., N Engl J Med 1994
Epstein-Barr Virus and Lymphoma in IBD

B-cell lymphoma

EBV in-situ hybridization

Dayharsh et al, Gastroenterology 2002
Epstein-Barr Virus and immunomodulator therapy

138 Crohn’s patients with serial EBV viral load measurements

2 pts had viral loads in dangerous range (i.e., risk for lymphoma)

No clear relationship between immunosuppressive therapy and EBV loads

Reijasse et al, Inflamm Bowel Dis 2004
Lymphomas in 30,000 rheumatoid arthritis patients treated with methotrexate: a 3-year prospective study in France


NLH (18 observed)
Effect of immunomodulators on colorectal cancer/dysplasia

No evidence of increased or decreased risk of CRC and/or dysplasia

Risk of Other Cancers With AZA/6MP

- Non-melanoma skin cancer, especially squamous cell cancer
  - In transplant literature, RR is 6 to 65
  - Might increase further with addition of ciclosporin

Use of immunosuppressants is associated with a higher incidence of abnormal Pap smears in women with IBD. Kane S et al. DDW 2006.

Abnormal Pap smears, cervical dysplasia and immunomodulator therapy in women with IBD. Venkatesan T et al. DDW 2006

Conclusions

- Tolerance of immunomodulators in the “real world” may not be as good as RCT data (22 – 28% withdrawal rates with AZA/6MP).

- Immunomodulators are associated with an increased risk of opportunistic infections, a risk that increased when they are used in combination.

- Most hepatotoxicity of AZA/6MP is mild and reversible but rarely more serious injury may occur.

- Relative risk of lymphoma with immunomodulator use is likely increased, up to fourfold - absolute risk remains low.

- In most situations, benefit of IM outweighs the risk.

- More studies needed.
Immunomodulators in IBD: the « real world » experience

- A cross-sectional nationwide French cohort
- Originally designed to prospectively assess the risk of cancers associated with the use of immunomodulators and biologics in IBD.
- 819 French gastroenterologists included in the cohort all consecutive IBD patients seen in their practice between May 2004 and May 2005.

Beaugerie et al. DDW 2006
Careful monitoring of side-effects is critical (often not done)!

www.StrangeCosmos.com