When to Use Immunomodulators in IBD?

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Consulting Professor, Duke University Medical Center, USA
OBJECTIVES

• Review the role of IMM in the treatment of IBD:
  – Crohn’s disease
  – Ulcerative colitis

• NOT COVERED:
  – Dosing & therapeutic drug monitoring
  – Adverse events, infectious or neoplastic complications
Use of Immunomodulators (IMMs) in IBD

- IMMs are well established in the treatment of IBD
- Used by 77-93% of gastroenterologists in Europe & North America\(^1,2\)
- Thiopurines used in practice by all surveyed Swedish GI physicians for multiple indications in CD and UC\(^3\)
- Azathioprine was the first-choice thiopurine (97%)\(^3\)

Crohn’s Disease
Impact of IMMs in Crohn’s Disease

A Tale of two Outcomes?

✓ Reduced surgery rates in cohort studies¹,²
☐ No convincing surgical benefit with thiopurines in large population-based study³
✓ Improved remission with early 6MP in pediatric CD⁴
☐ No benefit of early azathioprine in adults⁵,⁶
✓ 50% mucosal healing rates with azathioprine in ileal disease and 70% in colonic disease⁷
☐ Low mucosal healing rates in SONIC⁸

IMMs in CD
A Tale of Two Outcomes?
Ecco Guideline/Consensus Paper

3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn’s Disease 2016: Part 1: Diagnosis and Medical Management
Induction of Remission in CD: AZA/6MP vs. Placebo

## Should Thiopurines (AZA/6-MP) Versus Placebo Be Used for Adults With Active (Moderate to Severe) CD (CDAI 220–450)?

<table>
<thead>
<tr>
<th>Study event rates (%)</th>
<th>With thiopurines (AZA/6-MP)</th>
<th>With control</th>
<th>Relative effect (95% CI)</th>
<th>Anticipated absolute effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>115/183 (62.8)</td>
<td>102/197 (51.8)</td>
<td>RR, 0.87 (0.71–1.06)</td>
<td>628 per 1000</td>
<td>82 fewer per 1000 (from 182 fewer to 38 more)</td>
</tr>
</tbody>
</table>

AGA Technical Review

Methotrexate for Induction of Remission in CD

Should Methorexate (MTX) Versus Placebo Be Used for Adults With Active (Moderate to Severe) CD (CDAI 220–450)?

<table>
<thead>
<tr>
<th>Study event rates (%)</th>
<th>Relative effect (95% CI)</th>
<th>Anticipated absolute effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>With control</td>
<td>With MTX</td>
<td>RR, 0.82 (0.65–1.03)</td>
</tr>
<tr>
<td>58/73 (79.5)</td>
<td>76/120 (63.3)</td>
<td>795 per 1000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>143 fewer per 1000 (from 278 fewer to 24 more)</td>
</tr>
</tbody>
</table>

Efficacy of AZA/6MP vs. Placebo for Steroid-Sparing Effect in Active CD

Methotrexate in Steroid-Dependent CD

North American Crohn’s Study Group

MTX for Maintenance of Remission

Patients who entered remission after 16 to 24 weeks of treatment with 25 mg of methotrexate given intramuscularly once weekly.

The Earlier, the Better?
6-MP and Prednisone in Children with Newly Diagnosed CD

Is Early Azathioprine Effective in Adults?

Posthoc analysis: significantly lower rate of moderate-severe relapse (CDAI>220) with azathioprine compared with placebo (11.8% vs. 30.2%)

Secondary outcomes: Reduced perianal surgery in the azathioprine group at month 36 (4% ± 3% vs. 18% ± 6% for the conventional group; P = .036)

Recent (<8 wks) diagnosis

Diagnosis <6 months 1/3 not treated with steroids at inclusion
The Flip Argument

Thiopurines
Remission after Azathioprine Withdrawal

- Duration of disease (years): 10.2 (7.3-15.2)
- Duration of remission (years): 5.3 (4.0-6.4)
- Duration of azathioprine (years): 5.7 (4.4-7.1)

“if AZA is well tolerated [and effective], it should not be interrupted”

Combination with anti-TNF
# Immunogenicity of TNF Antagonists with and without Concomitant IMMs

<table>
<thead>
<tr>
<th></th>
<th>Patients, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Episodic Maintenance</td>
</tr>
<tr>
<td></td>
<td>IMM-</td>
</tr>
<tr>
<td><strong>Infliximab</strong>¹</td>
<td></td>
</tr>
<tr>
<td>(CD 5mg/kg)</td>
<td>38%</td>
</tr>
<tr>
<td>(CD 10mg/kg)</td>
<td></td>
</tr>
<tr>
<td><strong>Infliximab</strong>²</td>
<td></td>
</tr>
<tr>
<td>(UC5mg/kg)</td>
<td></td>
</tr>
<tr>
<td>(UC 10mg/kg)</td>
<td></td>
</tr>
<tr>
<td><strong>Certolizumab</strong>³</td>
<td></td>
</tr>
<tr>
<td>(PRECISE I)</td>
<td></td>
</tr>
<tr>
<td><strong>Certolizumab</strong>⁴</td>
<td></td>
</tr>
<tr>
<td>(PRECISE II)</td>
<td>24%</td>
</tr>
<tr>
<td><strong>Adalimumab</strong>⁵</td>
<td></td>
</tr>
<tr>
<td>(RA, all doses)</td>
<td></td>
</tr>
<tr>
<td><strong>Adalimumab</strong>⁶</td>
<td></td>
</tr>
<tr>
<td>(CLASSIC II)</td>
<td></td>
</tr>
<tr>
<td><strong>Golimumab</strong>⁷</td>
<td></td>
</tr>
<tr>
<td>(RA)</td>
<td></td>
</tr>
</tbody>
</table>

# Infliximab (IFX) Levels in Patients Taking Concomitant Immunomodulators

## Increased IFX blood levels in IMM takers

<table>
<thead>
<tr>
<th></th>
<th>No immunosuppressives</th>
<th>Immunosuppressives</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IFX levels</strong></td>
<td>2.42 µg/mL</td>
<td>6.45 µg/mL†</td>
</tr>
<tr>
<td>(median + IQR)</td>
<td>(1-10.8)</td>
<td>(3-11.6)</td>
</tr>
<tr>
<td><strong>Max IFX</strong></td>
<td>21 µg/mL</td>
<td>33.4 µg/mL</td>
</tr>
</tbody>
</table>

†p=0.065

Azathioprine, Infliximab or Combination Therapy for Crohn’s Disease (SONIC)

Primary endpoint: Corticosteroid-free clinical remission at week 26

- Naïve to IMM & IFX
- Median disease duration 2.4 years

Steroid-Free Remission by Infliximab Trough Level: Week 30 Results


**Median infliximab concentration**

**SFR at week 26 by w30 IFX TL**

<table>
<thead>
<tr>
<th>Serum IFX Concentration (µg/ml)</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFX</td>
<td>19/32</td>
</tr>
<tr>
<td>IFX + AZA</td>
<td>13/23</td>
</tr>
<tr>
<td>&gt; 0-1</td>
<td>43/59</td>
</tr>
<tr>
<td>&gt; 1.3</td>
<td>36/49</td>
</tr>
<tr>
<td>&gt; 3-6</td>
<td>72</td>
</tr>
<tr>
<td>&gt; 6</td>
<td>72</td>
</tr>
</tbody>
</table>

*Serum IFX Concentration* (µg/ml)
Azathioprine, Infliximab or Combination Therapy for Crohn’s Disease (SONIC)

Mucosal Healing at week 26

Proportion of patients (%)

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Proportion</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZA + placebo</td>
<td>16.5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IFX + placebo</td>
<td>30.1%</td>
<td>0.023</td>
</tr>
<tr>
<td>IFX + AZA</td>
<td>43.9%</td>
<td>0.055</td>
</tr>
</tbody>
</table>

Azathioprine vs. Budesonide Following Corticosteroid-induced Clinical Remission

Mean CDAI at enrollment = 130±15

Mean disease duration < 2 years

Mucosal Healing with Aza vs. Budesonide after Steroid-Induced Clinical Remission

Moderate to severe CD (CDAI 220-450) for at least 6 weeks and naïve to IMM and anti-TNFs:
- Steroid-dependent with CDAI > 220 after reduction of steroid dose
- Considered for a 2nd dose of steroids within 12 months
- No response to ≥4 wks of either 5-ASA or budesonide

At randomization, 76.5% of the Aza group were not on any steroids

COMMIT: Infliximab ± Methotrexate in CD

Patients who had *initiated prenisone* (15–40 mg/day) for active symptoms within 6 weeks of the screening visit were eligible.

- Mean disease duration >9 years; 50% had prior surgery
- Less immunogenicity and higher IFX levels with MTX vs. PBO

Post-Operative CD
## Azathioprine for the Prevention of Postoperative Recurrence of CD

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Mean difference (CI 95%) with control arms (%)</th>
<th>p</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical recurrence (1 year)</td>
<td>8 (1-15)</td>
<td>0.021</td>
<td>13</td>
</tr>
<tr>
<td>Severe endoscopic recurrence (i2-i4)</td>
<td>15 (1.8-29)</td>
<td>0.026</td>
<td>7</td>
</tr>
</tbody>
</table>

NNT = number needed to treat

POCER: Should We Bet on Thiopurines?

POCER: Active Care is Associated with Reduced Endoscopic Recurrence

Thiopurine group: POR ≥i₂: 45% at 6 mo

Post-Operative Endoscopic Recurrence ($\geq i_2$) at 2 Years

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Proportion of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesalamine</td>
<td>83.3</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>64.7</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>6.3</td>
</tr>
</tbody>
</table>

Ulcerative Colitis
Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 2: Current Management

Marcus Harbord, a, t, Rami Eliakim, b, # Dominik Bettenworth, c
Konstantinos Karmiris, d Konstantinos Katsanos, e Uri Kopylov, f
Torsten Kucharzik, g Tamás Molnár, h Tim Raine, i Shaji Sebastian, j
Helena Tavares de Sousa, k Axel Dignass, l, t Franck Carbonnel, m, t
for the European Crohn’s and Colitis Organisation [ECCO]
Thiopurines for Maintenance of Remission in UC

Analysis 1.1. Comparison 1 Azathioprine versus placebo, Outcome 1 Failure to maintain remission.

Review: Azathioprine and 6-mercaptopurine for maintenance of remission in ulcerative colitis

Comparison: 1 Azathioprine versus placebo

Outcome: 1 Failure to maintain remission

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>AZA n/N</th>
<th>Placebo n/N</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hawthorne 1992</td>
<td>12/33</td>
<td>20/34</td>
<td></td>
<td>26.1%</td>
<td>0.62 [0.36, 1.05]</td>
</tr>
<tr>
<td>Jewell 1974</td>
<td>24/40</td>
<td>31/40</td>
<td></td>
<td>41.1%</td>
<td>0.77 [0.57, 1.05]</td>
</tr>
<tr>
<td>Sood 2000</td>
<td>11/25</td>
<td>15/25</td>
<td></td>
<td>19.9%</td>
<td>0.73 [0.42, 1.27]</td>
</tr>
<tr>
<td>Sood 2002</td>
<td>4/17</td>
<td>10/18</td>
<td></td>
<td>12.9%</td>
<td>0.42 [0.16, 1.10]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>115</td>
<td>117</td>
<td></td>
<td>100.0%</td>
<td>0.68 [0.54, 0.86]</td>
</tr>
</tbody>
</table>

Total events: 51 (AZA), 76 (Placebo)
Heterogeneity: $\chi^2 = 1.85$, df = 3 ($P = 0.60$); $I^2 = 0.0$
Test for overall effect: $Z = 3.16$ ($P = 0.0016$)
Test for subgroup differences: Not applicable

Azathioprine vs. 5-ASA in Steroid-Dependent UC

Success defined as induction of clinical and endoscopic remission and steroid discontinuation

OR = 4.78 (1.57-14.5)


Intent to Treat

- Azathioprine (AZA): 19/36 (53%) with P = 0.006
- 5-ASA: 7/36 (19%)

Per Protocol

- Azathioprine (AZA): 19/33 (58%) with P = 0.003
- 5-ASA: 7/33 (21%)
Withdrawal of Azathioprine in UC

Stopped AZA for reasons other than relapse (physician or patient choice after a period of remission (73%), or drug-related adverse events (27%)) and who had been in steroid-free remission for at least 3 months at the time of drug withdrawal
Methotrexate in Steroid-Dependent UC (METEOR)

Primary endpoint was success at week 16 defined as a Mayo score ≤2 with no item ≥1, complete steroid withdrawal with a forced tapering regimen, and no need for other IMM, anti-TNF or colectomy

- Median dose of prednisone at inclusion: 25mg/d
- Improved clinical remission without steroids (41.7% MTX vs. 23.5% PBO; p=0.04)
- Mucosal healing not different (35% MTX vs. 25.5% PBO)
- More nausea and vomiting with MTX (21.7% vs. 3.9%; P=0.006)

Combination with anti-TNF
Infliximab, Azathioprine, or Combination for Moderate to Severe UC (UC SUCCESS)

- Study terminated prematurely (40% of the enrollment target reached)
- Patients not responding to AZA by week 8 were denoted as failure of therapy and given additional rescue IFX

Steroid-Free Remission at Week 16 (%)

- AZA (N=76) 24% (n=18)
- IFX (N=77) 22% (n=17)
- IFX + AZA (N=78) 40% (n=31)

Use of azathioprine in IBD: modern aspects of an old drug

Edouard Louis, Peter Irving, Laurent Beaugerie


Thiopurine Treatment in Ulcerative Colitis: A Critical Review of the Evidence for Current Clinical Practice

Sara van Gennep, MD,* Nanne K. de Boer, MD, PhD, Geert R. D’Haens, MD, PhD,* and Mark Löwenberg, MD, PhD*

Inflamm Bowel Dis 2018;24:67-77.

The Basics of IBD Therapy

Dig Dis 2016;34:125–131
DOI: 10.1159/000443127

When to Start Immunomodulators in Inflammatory Bowel Disease?

Ala I. Sharara

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<table>
<thead>
<tr>
<th>Indication</th>
<th>RR (95% CI)</th>
<th>Quality of Evidence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Crohn’s Disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroid-sparing (TP/MTX)</td>
<td>3.69 (2.15-6.42) (TP)[7] 1.95 (1.09-3.48) (MTX)[40]</td>
<td>Low</td>
<td>Early use not superior in adults[9,10] Use IM methotrexate 25mg/wk Oral MTX not effective[43]</td>
</tr>
<tr>
<td>Maintenance of remission (TP/MTX)</td>
<td>2.32 (1.55-3.49) (TP)[7] 1.67 (1.05-2.67) (MTX)[43]</td>
<td>Moderate</td>
<td>Continuing Rx prevents relapse (RR=0.39; 95% CI=0.21-0.74)[6] IM MTX 15mg/wk after remission by steroids/MTX[41]</td>
</tr>
<tr>
<td>Maintenance of surgically-induced remission (TP)</td>
<td>Risk of relapse 0.74 (0.58-0.94)[11]</td>
<td>Low</td>
<td>Severe endoscopic (≥i2) recurrence: 45% at 6 mo &amp; 65% at 2 years[13-15]</td>
</tr>
<tr>
<td>Combination therapy with infliximab (TP)</td>
<td>Risk of failure to achieve remission 0.78 (0.62-0.97)[29]</td>
<td>Moderate</td>
<td>Early CD naïve to both agents ↓ immunogenicity &amp; CRP  ↑ infliximab levels</td>
</tr>
<tr>
<td><strong>Ulcerative Colitis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maintenance of steroid-induced remission (TP)</td>
<td>Risk of failure to maintain remission 0.68 (0.54-0.86)[19]</td>
<td>Low</td>
<td>Response should be evaluated as early as 10-12 weeks[20]</td>
</tr>
</tbody>
</table>
Take Home Message

- IMM modestly effective in **steroid-dependent disease** & for **maintenance of remission** in CD (TP/MTX) & UC (TP)
- IMM are associated with reduced immunogenicity and higher anti-TNF levels (TP/MTX)
- **Combination with anti-TNF agents (IFX)** in early CD improves outcome in IMM & anti-TNF naïve patients (TP)
- IMM have “several advantages including **low cost** and quality and **stability of remission** in responders”
- Improved selection of patients for IMM, better timing and optimization needed to enhance **benefit:risk profile**

TP=Thiopurines; MTX= Methotrexate
When to Use Immunomodulators in IBD?

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