Azathioprine for Induction and Maintenance of Remission in Crohn’s Disease

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Objectives

• Azathioprine as induction and maintenance therapy for CD and UC

• Results of AZTEC and GETAID trials

• To review the evidence for use of combination therapy with an immunosuppressive and an anti-TNF biologic in patients with IBD

• To review the evidence regarding adverse effects associated with azathioprine
NCCDS: Cumulative Remission During Therapy With Azathioprine for Active Crohn’s Disease

NCCDS = National Cooperative Crohn's Disease Study.
Summers. Gastroenterology. 1979
AZA/6-MP versus Placebo or Control
Induction of Clinical Remission

1.1.1 Azathioprine

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>AZA or 6-MP Events</th>
<th>Total</th>
<th>Placebo/Control Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panés 2013</td>
<td>38</td>
<td>68</td>
<td>41</td>
<td>63</td>
<td>20.0%</td>
<td>0.88 [0.67, 1.16]</td>
</tr>
<tr>
<td>Reinisch 2008</td>
<td>25</td>
<td>52</td>
<td>15</td>
<td>29</td>
<td>10.1%</td>
<td>0.93 [0.59, 1.46]</td>
</tr>
<tr>
<td>Cosnes 2013</td>
<td>58</td>
<td>65</td>
<td>60</td>
<td>67</td>
<td>37.2%</td>
<td>1.00 [0.89, 1.12]</td>
</tr>
<tr>
<td>Candy 1995</td>
<td>24</td>
<td>33</td>
<td>19</td>
<td>30</td>
<td>15.0%</td>
<td>1.15 [0.81, 1.62]</td>
</tr>
<tr>
<td>Summers 1979</td>
<td>21</td>
<td>59</td>
<td>20</td>
<td>77</td>
<td>8.3%</td>
<td>1.37 [0.82, 2.28]</td>
</tr>
<tr>
<td>Ewe 1993</td>
<td>16</td>
<td>21</td>
<td>8</td>
<td>21</td>
<td>6.4%</td>
<td>2.00 [1.10, 3.63]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td>183</td>
<td>163</td>
<td></td>
<td></td>
<td>1.07 [0.90, 1.27]</td>
</tr>
</tbody>
</table>

Total events = 183, Total = 163
Heterogeneity: Tau² = 0.02; Chi² = 8.34, df = 5 (P = 0.12); I² = 43%
Test for overall effect: Z = 0.73 (P = 0.46)

1.1.2 6-Mercaptopurine

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Events</th>
<th>Total</th>
<th>Placebo/Control</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oren 1997</td>
<td>9</td>
<td>32</td>
<td>6</td>
<td>26</td>
<td>3.1%</td>
<td>1.22 [0.50, 2.98]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>32</td>
<td>6</td>
<td>26</td>
<td>26</td>
<td>3.1%</td>
<td>1.22 [0.50, 2.98]</td>
</tr>
</tbody>
</table>

Total events = 9, Total = 6
Heterogeneity: Not applicable
Test for overall effect: Z = 0.43 (P = 0.66)

Total (95% CI) = 330, 100.0%
Total events = 192, 169
Heterogeneity: Tau² = 0.01; Chi² = 9.13, df = 6 (P = 0.17); I² = 34%
Test for overall effect: Z = 0.77 (P = 0.44)
Test for subgroup differences: Chi² = 0.08, df = 1 (P = 0.78), I² = 0%

Chande 2014a
Efficacy of Azathioprine as Maintenance Therapy in Adults With Refractory Crohn’s Disease

Graph showing the percentage of patients still in remission over the duration of the trial.

- Placebo (N=30)
- AZA 2.5 mg/kg per day (N=33)

* Remission induced by prednisolone tapered over 12 wk

6-Mercaptopurine for Maintenance of Remission in Moderate-to-Severe Pediatric Crohn’s Disease

At baseline, patients received prednisone plus either 6-MP or placebo. Steroids were tapered after induction of remission.

Top Down Therapy With Azathioprine + Prednisone versus Prednisone in Adults with Newly Diagnosed Crohn’s Disease

Sustained steroid free remission

Survival free of relapse

Panes J. Gastroenterology 2013
Top Down Therapy With Azathioprine + Prednisone versus Step Up Therapy with Prednisone and then Azathioprine in Adults with Newly Diagnosed Crohn’s Disease

![Graph showing proportion of patients in remission over months after randomization. The graph compares early azathioprine and conventional management.](image-url)
AZA/6-MP versus Placebo
Outcome = Maintenance of Clinical Remission

### 1.1.2.1 Azathioprine dose 2.5 mg/kg/day
- **Panes 2013**
  - Events: 46
  - Total: 69
  - Placebo: 36
  - Total: 63
  - Weight: 19.9%
  - Risk Ratio: 1.19 [0.90, 1.55]
- **Summers 1979**
  - Events: 16
  - Total: 19
  - Placebo: 15
  - Total: 20
  - Weight: 7.7%
  - Risk Ratio: 1.12 [0.82, 1.55]
- **Subtotal (95% CI)**
  - Events: 62
  - Total: 51
  - Weight: 27.8%
  - Risk Ratio: 1.17 [0.94, 1.44]

### 1.1.2.2 Azathioprine dose 2.0 mg/kg/day
- **O’Heen 2008a**
  - Events: 37
  - Total: 40
  - Placebo: 34
  - Total: 41
  - Weight: 17.9%
  - Risk Ratio: 1.12 [0.96, 1.31]
- **Lécrine 2005**
  - Events: 38
  - Total: 38
  - Placebo: 36
  - Total: 43
  - Weight: 18.4%
  - Risk Ratio: 1.13 [0.98, 1.32]
- **O’Donoghue 1978**
  - Events: 13
  - Total: 23
  - Placebo: 8
  - Total: 27
  - Weight: 3.9%
  - Risk Ratio: 1.91 [0.96, 3.70]
- **Rosenberg 1975**
  - Events: 7
  - Total: 10
  - Placebo: 4
  - Total: 10
  - Weight: 2.1%
  - Risk Ratio: 1.75 [0.74, 4.14]
- **Wollamby 1971**
  - Events: 4
  - Total: 5
  - Placebo: 2
  - Total: 5
  - Weight: 1.1%
  - Risk Ratio: 2.00 [0.63, 6.36]
- **Subtotal (95% CI)**
  - Events: 99
  - Total: 94
  - Weight: 43.3%
  - Risk Ratio: 1.25 [1.09, 1.42]

### 1.1.2.3 Azathioprine dose 1.0 mg/kg/day
- **Summers 1979**
  - Events: 37
  - Total: 54
  - Placebo: 65
  - Total: 101
  - Weight: 24.0%
  - Risk Ratio: 1.06 [0.84, 1.34]
- **Subtotal (95% CI)**
  - Events: 54
  - Total: 101
  - Weight: 24.0%
  - Risk Ratio: 1.06 [0.84, 1.34]

### 1.1.2.4 6-Mercaptopurine 50mg/day
- **Hanauer 2004**
  - Events: 24
  - Total: 47
  - Placebo: 9
  - Total: 40
  - Weight: 5.2%
  - Risk Ratio: 2.27 [1.20, 4.30]
- **Subtotal (95% CI)**
  - Events: 47
  - Total: 40
  - Weight: 5.2%
  - Risk Ratio: 2.27 [1.20, 4.30]

### Total (95% CI)
- **Total events**
  - Placebo: 306
  - AZA or 6-MP: 350
  - Total: 100.0%
  - Risk Ratio: 1.23 [1.11, 1.37]

- **Heterogeneity:** Chi² = 10.99, df = 8 (P = 0.20); I² = 27%
- **Test for overall effect:** Z = 3.89 (P = 0.0001)
- **Test for subgroup differences:** Chi² = 5.20, df = 3 (P = 0.16), I² = 42.4%

Chande 2014b
Rate of Surgery for Crohn’s Disease and the Use of Immunosuppressives in Paris Over 3 Decades

Use of Immunosuppressives

Need for Surgery

6-Mercaptopurine and Mesalamine for Prevention of Post-Operative Recurrence of Crohn’s Disease

Estimate of Efficacy of AZA for Treatment Success in UC Patients: Meta-Analysis

Pooled RR Estimate Across 5 Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk ratio (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ardizzone 2006</td>
<td>2.71 (1.30, 5.65)</td>
<td>17.3</td>
</tr>
<tr>
<td>Sood 2002</td>
<td>1.72 (0.96, 3.07)</td>
<td>21.4</td>
</tr>
<tr>
<td>Sood 2003</td>
<td>0.68 (0.31, 1.50)</td>
<td>15.9</td>
</tr>
<tr>
<td>Sood 2000</td>
<td>1.06 (0.71, 1.58)</td>
<td>27.0</td>
</tr>
<tr>
<td>Jewell 1974</td>
<td>1.78 (0.89, 3.54)</td>
<td>18.4</td>
</tr>
<tr>
<td>Overall (95% CI)</td>
<td>1.42 (0.93, 2.17)</td>
<td></td>
</tr>
</tbody>
</table>

What is the Evidence for Use of Combination Therapy with an Immunosuppressive and an Anti-TNF Biologic in Patients with IBD?

- Combination therapy
  - More effective in prospective randomized trials
  - Reduces rates of antibody formation
  - Results in higher blood concentrations of the biologic
  - Similar side effect profile to monotherapy
SONIC: Clinical Remission without Corticosteroids at Week 26

Primary End Point

Proportion of Patients (%)

- AZA + placebo
- IFX + placebo
- IFX + AZA

SONIC: Mucosal Healing at Week 26

Infliximab, Azathioprine, or Infliximab + Azathioprine for Treatment of Moderate to Severe UC: UC SUCCESS Trial

Primary End Point: Steroid-Free Remission at Week 16

- AZA: 24% (18/76)
- IFX: 22% (17/77)
- IFX + AZA: 40% (31/78)

$P=0.017$

$P=0.813$

$P=0.032$

UC, ulcerative colitis

Panaccione R et al. Gastroenterology 2014
Infliximab, Azathioprine, or Infliximab + Azathioprine for Treatment of Moderate to Severe UC: UC SUCCESS Trial

**Major Secondary End Point: Response at Week 16**

- **AZA**: 50% (38/76) with P=0.018
- **IFX**: 69% (53/77) with P=0.001
- **IFX + AZA**: 77% (60/78) with P=0.514

Infliximab, Azathioprine, or Infliximab + Azathioprine for Treatment of Moderate to Severe UC: UC SUCCESS Trial

Secondary End Point: Mucosal Healing at Week 16

- AZA: 37% (28/76)
- IFX: 55% (42/77)
- IFX + AZA: 63% (49/78)

Panaccione R et al. Gastroenterology 2014
SONIC: Immunogenicity Results at Week 30*

*Patients who had 1 or more PK samples obtained after their first study agent administration were included in the analysis. PK data at Wk 30 was not available for 1 patient treated with AZA + placebo, 3 patients treated with IFX + placebo, and 4 patients treated with AZA + IFX.

Sandborn WJ. Unpublished data.
ACCENT 1 IFX in Crohn’s Disease: Median Serum IFX Trough Concentrations Over Time Stratified by Immunosuppressive Therapy

ACCENT 1 IFX in Crohn’s Disease: Serum IFX Trough Concentration at the Last Clinical Visit Stratified by Immunosuppressive Therapy

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.

Adverse Events with Azathioprine
Toxicity of Azathioprine and 6-Mercaptopurine in Inflammatory Bowel Disease

- Overall toxicity 15%
  - Pancreatitis 3.3%
  - Bone marrow depression 2%
  - Allergic reactions 2%
  - Drug hepatitis 0.3%
  - Infectious complications 7.4%
  - Malignant neoplasm 3.1%
- Lymphoma
  - Meta-analysis of 6 studies showed that AZA/6MP treatment is associated with 4-fold increase (SIR = 4.2 [95% CI = 2.1–7.5]) in risk of EBV-positive lymphoma

Present DH et al Ann Int Med. 1989;111:641
Kandiel A et al. Gut. 2005;54;1121
CESAME: Incidence rates of lymphoproliferative disorders according to azathioprine exposure grouped by age at entry in the cohort

Beaugerie L. Lancet 2009
## 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
- Mean age 52, 62% male
- 10/13 exposed to IM* (really a study of combo Rx)

### NHL rate per 10,000 SIR 95% CI

<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>

*not reported in 2

Siegel et al, CGH 2009;7:874
Risk of Skin Cancer Associated with Thiopurines (CESAME)

- 19,486 IBD patients
- 32 cases of skin cancer (20 basal cell, 12 squamous)

Look at denominator
**SONIC: Summary of Adverse Events Through Week 50**  
All Randomized Patients

<table>
<thead>
<tr>
<th></th>
<th>AZA + placebo (n=161)</th>
<th>IFX + placebo (n=163)</th>
<th>IFX + AZA (n=179)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts with ≥1 AE, n (%)</td>
<td>144 (89.4%)</td>
<td>145 (89.0%)</td>
<td>161 (89.9%)</td>
</tr>
<tr>
<td>Pts with ≥1 SAE, n (%)</td>
<td>43 (26.7%)</td>
<td>39 (23.9%)</td>
<td><strong>27 (15.1%)</strong></td>
</tr>
<tr>
<td>Serious infections</td>
<td>9 (5.6%)</td>
<td>8 (4.9%)</td>
<td>7 (3.9%)</td>
</tr>
</tbody>
</table>

Tuberculosis: 1 patient treated with infliximab and azathioprine  
Colon cancer: 2 patients treated with azathioprine monotherapy  
Death: postcolectomy, in a patient treated with azathioprine monotherapy

Conclusions

• Azathioprine monotherapy is not effective for induction, it may be modestly effective for maintenance of steroid induced remission in patients with established Crohn’s disease
• Combination therapy is more effective than azathioprine or anti-TNF monotherapy for steroid-free remission and mucosal healing
• Combination therapy results in lower immunogenicity and higher anti-TNF antibody blood concentrations
• Monotherapy and combination therapy have similar rates of serious infection when considering the combined rates of BOTH disease related infections and opportunistic infections
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• Combination therapy is more effective than azathioprine or anti-TNF monotherapy for steroid-free remission and mucosal healing
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