Is There Still a Role for Azathioprine Monotherapy in the Treatment of IBD?

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Digestive Disease Institute
Virginia Mason Medical Center
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Objectives

• Review the role of thiopurines for:
  – Induction and maintenance therapy in CD
  – Maintenance therapy in UC
  – Post-operative prevention in CD

• Safety and economics data

• Identify appropriate indications for thiopurine therapy
AZA/6-MP as Maintenance Therapy in Crohn’s Disease after Steroid Induction

*Remission induced by prednisolone tapered over 12 wk.

Thiopurines in Crohn’s Disease 1980s-1990s

• 1979 NCCD study
  – Aza NOT effective for induction of remission

• 1980 single center study (n=83)
  – 6MP effective as induction/maintenance in CD
    • 67% 6-MP vs. 8% Pbo (p<0.001)
    • 31% vs. 6% in closing fistulas
    • 75% vs. 36% steroid sparing
  – Mean time to response: 3.1 months
    • 19% of patients took > 4 months

Summers et al. – Gastroenterol ’79; Present et al. – NEJM ‘80
Thiopurines for Induction and Maintenance of Remission in Crohn’s Disease
Aza/6-MP for Induction of Remission in Crohn’s Disease - Cochrane 2013-

• OR for treatment > 17 wks = 1.59 vs. 1.08 with < 17 wks (NS)

Chande et al. – Cochrane Database Syst Rev. ‘13
### Aza/6-MP for Steroid Sparing in Crohn’s Disease – Cochrane 2010

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment</th>
<th>Control</th>
<th>Peto Odds Ratio</th>
<th>Weight</th>
<th>Peto Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>Peto,Fixed,95% CI</td>
<td></td>
<td>Peto,Fixed,95% CI</td>
</tr>
<tr>
<td>Candy 1995</td>
<td>25/33</td>
<td>20/30</td>
<td>1.55 [0.52, 4.59]</td>
<td>25.9 %</td>
<td></td>
</tr>
<tr>
<td>Ewe 1993</td>
<td>16/21</td>
<td>8/21</td>
<td>4.57 [1.36, 15.27]</td>
<td>21.0 %</td>
<td></td>
</tr>
<tr>
<td>Klein 1974</td>
<td>2/13</td>
<td>2/13</td>
<td>1.00 [0.12, 8.08]</td>
<td>7.0 %</td>
<td></td>
</tr>
<tr>
<td>Present 1980</td>
<td>28/44</td>
<td>6/39</td>
<td>7.18 [3.00, 17.16]</td>
<td>40.3 %</td>
<td></td>
</tr>
<tr>
<td>Willoughby 1971</td>
<td>5/6</td>
<td>3/6</td>
<td>3.96 [0.90, 39.38]</td>
<td>5.8 %</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>117</strong></td>
<td><strong>109</strong></td>
<td><strong>3.69 [2.12, 6.42]</strong></td>
<td><strong>100.0 %</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 76 (Treatment), 39 (Control)
Heterogeneity: Chi² = 6.32, df = 4 (P = 0.18); I² = 37%
Test for overall effect: Z = 4.63 (P < 0.00001)
Test for subgroup differences: Not applicable

Prefontaine et al. – Cochrane Database Syst Rev. ‘10
# Aza/6-MP for Steroid Sparing in Crohn’s Disease – Cochrane 2013*

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>AZA or 6-MP</th>
<th>Placebo</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candy 1995</td>
<td>24/33</td>
<td>19/30</td>
<td>1.15 [0.81, 1.62]</td>
<td>65.7%</td>
</tr>
<tr>
<td>Ewe 1993</td>
<td>16/21</td>
<td>8/21</td>
<td>2.00 [1.10, 3.63]</td>
<td>21.8%</td>
</tr>
<tr>
<td>Klein 1974</td>
<td>2/13</td>
<td>2/13</td>
<td>1.00 [0.16, 6.07]</td>
<td>2.4%</td>
</tr>
<tr>
<td>Willoughby 1971</td>
<td>5/6</td>
<td>3/6</td>
<td>1.07 [0.69, 4.00]</td>
<td>10.1%</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>73</strong></td>
<td><strong>70</strong></td>
<td><strong>1.34 [1.02, 1.77]</strong></td>
<td><strong>100.0%</strong></td>
</tr>
</tbody>
</table>

Total events: 47 (AZA or 6-MP), 32 (Placebo)
Heterogeneity: Tau² = 0.0; Chi² = 2.93, df = 3 (P = 0.40); I² = 0.0%
Test for overall effect: Z = 2.07 (P = 0.039)
Test for subgroup differences: Not applicable

*After excluding the trial by Present et al. – NEJM ’80 due to cross-over design

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Chande et al. – Cochrane Database Syst Rev. ‘13

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[Virginia Mason]
Aza/6-MP for Maintenance of Remission in Crohn’s Disease

NNT for maintenance = 6

Prefontaine et al. – Cochrane Database Syst Rev. ‘10
Why the Heterogeneity in the Induction & Maintenance Trials?

• A dose-finding study with Aza/6-MP was terminated early, however ....
**Cochrane 2009: Maintenance w AZA in CD**

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Peto Odds Ratio</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azathioprine dose 2.5 mg/kg/day</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candy 1995</td>
<td>14/25</td>
<td>2/20</td>
<td>[7.12 [2.11, 23.99]]</td>
<td>18.3%</td>
</tr>
<tr>
<td>Summers 1979</td>
<td>16/19</td>
<td>15/20</td>
<td>[1.73 [0.37, 8.05]]</td>
<td>4.13</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>44</strong></td>
<td><strong>40</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azathioprine dose 2.0 mg/kg/day</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D’Haens 2007</td>
<td>18/32</td>
<td>9/29</td>
<td>[2.73 [1.00, 7.45]]</td>
<td>16.5%</td>
</tr>
<tr>
<td>Lemann 2005</td>
<td>38/40</td>
<td>36/43</td>
<td>[3.17 [0.80, 12.54]]</td>
<td>8.8%</td>
</tr>
<tr>
<td>O’Donoghue 1978</td>
<td>13/23</td>
<td>8/27</td>
<td>[2.95 [0.97, 9.00]]</td>
<td>9.8%</td>
</tr>
<tr>
<td>Rosenberg 1975</td>
<td>7/10</td>
<td>4/10</td>
<td>[3.16 [0.57, 17.62]]</td>
<td>7.1%</td>
</tr>
<tr>
<td>Willoughby 1971</td>
<td>4/5</td>
<td>2/5</td>
<td>[4.48 [0.41, 49.42]]</td>
<td>2.9%</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>110</strong></td>
<td><strong>114</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azathioprine dose 1.0 mg/kg/day</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Summers 1979</td>
<td>37/54</td>
<td>65/101</td>
<td>[1.20 [0.60, 2.41]]</td>
<td>34.5%</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>54</strong></td>
<td><strong>101</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Prefontaine et al. - Cochrane Database Syst Rev. 2009 Jan 21;(1)
Metabolism of AZA/6-MP

AZA → 6-MP → 6-thiouric acid

XO

HPRT

TPMT

6-MMP → 6-TGNs
Target 6-TGN Level to Optimize Efficacy: >235

Dubinsky MC et al. Gastroenterol2000;118:

Odds Ratio 5.0 for treatment response when 6-TGN > 235

P< 0.001
Association of 6-thioguanine nucleotide levels and IBD activity: a meta-analysis

Osterman MT. Gastroenterology 2006;130:1047-53.
Sonic: steroid-free remission at week 26

Steroid-free remission = CDAI <150 points

Colombel JF et al. NEJM 2010
Therapeutic Azathioprine Levels and Outcomes in CD: SONIC

Post-hoc analysis based on week 26 MCV value

* *p<0.005
t*p<0.05

Patients (%)

<table>
<thead>
<tr>
<th></th>
<th>Delta MCV &lt; 7</th>
<th>Delta MCV &gt; 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>CS-free remission</td>
<td>Aza monotherapy</td>
<td>Aza + IFX</td>
</tr>
<tr>
<td>Mucosal Healing</td>
<td>33.3%</td>
<td>26.7%</td>
</tr>
<tr>
<td></td>
<td>33.3%</td>
<td>63.6%</td>
</tr>
</tbody>
</table>

Bouguen et al. - Inflamm Bowel Dis 2015;21:606–614
Early “Top-Down” Therapy with Azathioprine Is Not More Effective than Placebo or Conventional Therapy in Crohn’s Disease

Figure 1. Actuarial probability of survival free of relapse defined as a CDAI score >175 in patients treated with azathioprine and placebo.

Figure 2. Proportion of patients in corticosteroid-free, anti-TNF-free remission per trimester over time. The concomitant proportions were significantly different only at trimester 3 (P < .05). Trimesters ended by a missing visit are excluded.

Early “top-down” Therapy with Azathioprine in Crohn’s Disease

The “Good”

**RAPID Study**
- Trend for lower steroid use
- Fewer peri-anal surgeries in top-down group (3% vs. 13%, p<0.05)

**AZTEC**
- Trend for lower steroid use
- Lower relapse rate in Aza group vs. placebo after 3 months of therapy (11.8% vs. 30.2%, p=0.01)

Early “top-down” Therapy with Azathioprine in Crohn’s Disease

The “Ugly”

**RAPID Study**
- Problems with recruitment
  - 5 years, 24 centers
- Open label
- Moderate-severe, “disabling” disease
  - Patients w fistulas, steroid-refractory, young
- Unconventional end-point
- No objective endpoints
- No real placebo arm
  - 60% of controls received Aza
- No dose optimization

**AZTEC Study**
- Problems with recruitment
  - Stopped early
- No objective endpoints
- No dose optimization

Time to Relapse Post-Azathioprine Withdrawal in IBD

• Multi-center retrospective trial

• 237 patients with UC & CD in stable remission on thiopurines for > 3 years (median = 6 ys)

*Kennedy NA et al - APT 2014:40;1313-2013*
Time to Relapse Post-Azathioprine Withdrawal in CD

Kennedy NA et al - APT 2014:40;1313-2013
Predictors of Relapse Post-Thiopurine Withdrawal

- WBC > 6 (HR 3.7)
- ↑ CRP (HR 3.2)
- WBC > 9 in UC (HR 6.7)

in Crohn’s Disease

Kennedy NA et al - APT 2014:40;1313-2013
Take Home Message

Especially if the disease is NOT in remission!
Withdrawal of Azathioprine in CD
Meta-analysis

Relapse rates at 12 months

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Azathioprine</th>
<th>Placebo/No azathioprine</th>
<th>Odds Ratio</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td></td>
<td>M-H, Random, 95% Cl</td>
</tr>
<tr>
<td>KIm 1999</td>
<td>24</td>
<td>84</td>
<td>36</td>
<td>0.71 [0.31, 1.62]</td>
</tr>
<tr>
<td>Lemann 2005</td>
<td>2</td>
<td>40</td>
<td>43</td>
<td>0.27 [0.05, 1.39]</td>
</tr>
<tr>
<td>O'Donoghue 1978</td>
<td>1</td>
<td>24</td>
<td>27</td>
<td>0.06 [0.01, 0.54]</td>
</tr>
<tr>
<td>Sokol 2010</td>
<td>9</td>
<td>94</td>
<td>47</td>
<td>0.19 [0.08, 0.46]</td>
</tr>
<tr>
<td>Vilien 2004</td>
<td>2</td>
<td>14</td>
<td>15</td>
<td>0.15 [0.02, 0.89]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>255</td>
<td>168</td>
<td>100.0%</td>
<td>0.25 [0.11, 0.58]</td>
</tr>
</tbody>
</table>

Total events: 38
Total control: 56

Heterogeneity: Tau² = 0.40; Chi² = 7.85, df = 4 (P = 0.10); I² = 49%
Test for overall effect: Z = 3.26 (P = 0.001)

NNT = 6

French H et al. – Dig Dis Sci ‘11
Thiopurine Use is Associated with a 40% Lower Risk of Surgery in Crohn’s Disease

<table>
<thead>
<tr>
<th>Group by</th>
<th>Study name</th>
<th>Hazard ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study population</td>
<td>Vernier-Massouille</td>
<td>0.51</td>
<td>0.33</td>
<td>0.78</td>
</tr>
<tr>
<td></td>
<td>Ramadas</td>
<td>0.47</td>
<td>0.27</td>
<td>0.80</td>
</tr>
<tr>
<td></td>
<td>Schaefer</td>
<td>0.80</td>
<td>0.50</td>
<td>1.29</td>
</tr>
<tr>
<td></td>
<td>Lakatos</td>
<td>0.40</td>
<td>0.19</td>
<td>0.86</td>
</tr>
<tr>
<td></td>
<td>Nguyen</td>
<td>1.18</td>
<td>0.90</td>
<td>1.55</td>
</tr>
<tr>
<td></td>
<td>Chatu</td>
<td>0.56</td>
<td>0.37</td>
<td>0.85</td>
</tr>
<tr>
<td></td>
<td>Pooled (population)</td>
<td>0.64</td>
<td>0.44</td>
<td>0.93</td>
</tr>
<tr>
<td>2.00</td>
<td>Picco</td>
<td>0.41</td>
<td>0.21</td>
<td>0.81</td>
</tr>
<tr>
<td>2.00</td>
<td>Peyrin-Biroulet</td>
<td>0.50</td>
<td>0.30</td>
<td>0.83</td>
</tr>
<tr>
<td>2.00</td>
<td>Gao</td>
<td>0.44</td>
<td>0.22</td>
<td>0.88</td>
</tr>
<tr>
<td>2.00</td>
<td>Camus</td>
<td>0.69</td>
<td>0.52</td>
<td>0.91</td>
</tr>
<tr>
<td>2.00</td>
<td>Pooled (hospital based)</td>
<td>0.57</td>
<td>0.45</td>
<td>0.73</td>
</tr>
<tr>
<td>Overall</td>
<td>Pooled (combined)</td>
<td>0.59</td>
<td>0.48</td>
<td>0.73</td>
</tr>
</tbody>
</table>

1= population-based study
2= hospital tertiary referral-based studies

Chatu S et al - Am J Gastroenterol 2014;109:409-16
# Predictors of Surgery within 5 Years of Crohn’s Diagnosis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate p-value</th>
<th>Multivariate p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age onset &gt; 18 vs. &lt; 18</td>
<td>0.73</td>
<td>0.60</td>
</tr>
<tr>
<td>Thiopurine use &gt; 12 mos vs. &lt; 12 mos</td>
<td>0.60</td>
<td>0.31</td>
</tr>
<tr>
<td>Steroids within 3 mos of dx</td>
<td>1.99</td>
<td>2.25</td>
</tr>
</tbody>
</table>

*Chatu S et al - Am J Gastroenterol 2014;109:409-16*
Thiopurines for Maintenance of Remission in Ulcerative Colitis
Steroid-dependent UC
Failure of 5-ASA
Azathioprine versus 5-ASA for Steroid-dependent UC

Treatment success defined as clinical remission (Powell-Tuck Index score of 0) and endoscopic remission (Baron Index score ≤1), plus steroid discontinuation

Azathioprine, Infliximab and Combo in Active Ulcerative Colitis: UC SUCCESS

Steroid-free remission at Week 16

Patients were biologic-naive with moderate-severe UC (Mayo score 6) who were failing corticosteroids and either naive to AZA, or had stopped AZA 3 months before entry.

AZA, azathioprine; IFX, infliximab.

Time to Relapse Post-Azathioprine Withdrawal in UC

Kennedy NA et al - APT 2014:40;1313-2013
Steroid-dependent UC
Failure of 5-ASA
Steroid-dependent UC
After 6 Months of Azathioprine + Allopurinol
Thiopurines for Post-operative Recurrence in Crohn’s Disease
TI Crohn’s Disease x 12 years
With Stricture + Fistula
Pre-op
6-MP vs. Mesalamine for Postoperative Recurrence in Crohn’s Disease

Hanauer et al. – Gastro ‘04
## AZA for Prevention of Post-operative Recurrence in Crohn’s disease

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Absolute Risk Reduction (%, 95% CI)</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>Clinical recurrence (2 years)</td>
<td>13 (2–24)</td>
<td>0.018</td>
<td>8</td>
</tr>
<tr>
<td>Endoscopic recurrence (1 year)</td>
<td>23 (9–37)</td>
<td>0.0016</td>
<td>4</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>

*Peyrin-Biroulet L et al. - Am J Gastroenterol 2009*
TI Crohn’s Disease
18 Months Post-op on Azathioprine

Rutgeerts score i0
Cost Utility of Thiopurine Therapy in IBD
Healthcare Costs of IBD Have Shifted from Hospitalization and Surgery to Medical Treatment

Anti-TNF use accounts for 64% and 31% of total costs in CD and UC

Van der Valke ME et al. - Gut 2012
Comparative Costs of Thiopurines

• With the same 1-year budget, one can treat effectively
  – 1 patient with anti-TNF alpha
  OR
  – 100 patients with Aza

Bourrier A, Seksik P, Cosnes J. - Current Drug Targets 2013
Safety of Azathioprine

• Lymphoma risk
  – NHL: absolute risk 1:2,000 (2-5x)
  – HSTCL (with anti-TNF)
    • Young males absolute risk 1:10,000
    • Overall population risk <1:20,000

• Increased risk of skin cancer ≈ 2-5 x

• Bone marrow suppression

Herrinton et al. – Am J Gastro ‘11; Kotlyar et al. – CGH ‘14; Beaugerie et al. – Gastro ‘13;
Long et al. – Gastro ‘12; Singh et al. – Gastro ‘11; Peyrin-Biroulet et al. – Gastro ‘11
Safety of Azathioprine

• No increased risk of infections when used alone
• No increased risk of new or recurrent solid organ cancers in patients with prior malignancy
• Safe during pregnancy and lactation

Lichtenstein G et al. - DDW 2010; Beaugerie et al. – Gut ‘14; Jharap et al. – Gut ‘14
AGA Guideline on the Use of Thiopurines, Methotrexate, and Anti–TNF-α Biologic Drugs for Induction and Maintenance of Remission in Crohn's Disease

- We Suggest **Against** Using Thiopurine Monotherapy to Induce Remission in Patients With Moderately Severe CD
  (Weak Recommendation, Moderate-Quality Evidence)

*Terdiman et al. - Gastroenterology. 2013;145(6):1459-63*
AGA Guideline on the Use of Thiopurines, Methotrexate, and Anti–TNF-α Biologic Drugs for Induction and Maintenance of Remission in Crohn's Disease

• We Recommend Using Thiopurines Over No IMM Therapy to **Maintain** a Corticosteroid-Induced Remission in Patients With Crohn’s Disease

*(Strong Recommendation, Moderate-Quality Evidence)*

*Terdiman et al. - Gastroenterology. 2013;145(6):1459-63*
Crohn’s Disease Evaluation and Treatment Clinical Decision Tool

Candidates for thiopurine therapy (low-risk):

• Age at diagnosis > 30
• Limited anatomic involvement
  – Ileal, ileo-colonic
• Response to steroids
• No perianal or severe rectal disease
• No penetrating complications

Sandborn et al. – Gastroenterol. ’14
• www.virginiamason.org/ibdcenter

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