Systemic Medications for the Dermatology Toolbox: Azathioprine

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Faculty Disclosure Information

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**Off-label use of medications discussed**
Azathioprine and the Skin

- FDA approved for prevention of renal transplant rejection and rheumatoid arthritis
- In dermatology, it is used for:
  - Autoimmune bullous disorders
  - Atopic dermatitis and other eczematous dermatitis
  - Photodermatoses
  - Connective tissue disorders incl. SLE
  - Psoriasis
  - Behcet’s disease
  - GVHD
Pharmacokinetics

• Mechanism of action
  o 6-mercaptopurine analog that inhibits purine synthesis – lymphocytes rely on *de novo* synthesis and more selectively affected
  o Also affects T-cell activation by blocking the CD28 costimulatory signal
• Well-absorbed after oral intake, extensively metabolized in RBCs and liver, small remainder excreted in urine
• Clinical improvement - at least 6-8 weeks
Overview of Thiopurine Metabolism

Azathioprine

- Concern for profound marrow suppression – genetic polymorphisms in Thiopurine Methyl Transferase (TPMT) are important
  - 1 in 300 individuals homozygous for low activity alleles, 10% have intermediate activity
  - Low activity correlates with higher risk of suppression
- Use red blood cell TPMT activity to guide dosing
  - Normal activity: start 2.5mg/kg/d, ↑ by 0.5mg/kg/d prn
  - Intermediate: start 1 mg/kg/d, ↑ by 0.25mg/kg/d prn
  - Low: generally not recommended to use, although this has been done with careful monitoring of cell counts
Drug Dosing

• Basing on TPMT activity level appears to significantly reduce myelosuppression risk
• 50mg increments to 100-250mg – sometimes adults may not need as high a dose as children
• Maximum dose that I use is 3.5, and rarely, 4.0 mg/kg/d
• Monitoring
  o Baseline: CBC, renal and liver function, TB testing, hepatitis B and C, HIV
  o Follow-Up: CBC, renal and liver function at 2-4 weeks then monthly x 2-3 months, once dose stable Q 3-4 months; repeat infectious tests annually
Contraindications

• Demonstrated hypersensitivity to azathioprine
  o Fever, malaise, diarrhea, rash, myalgias, ↑ liver enzymes, occ hypotension; usually in the first several weeks of tx
• Pregnancy Category D, generally avoid during lactation
• Drug Interactions
  o Dose reduction needed with allopurinol
  o May have higher risk of cytopenia with aminosalicylates, cotrimoxazole, ACE inhibitors, ribavirin
  o Can inhibit warfarin effect
WARNING

MALIGNANCY

Chronic immunosuppression with IMURAN, a purine antimetabolite increases risk of malignancy in humans. Reports of malignancy include post-transplant lymphoma and hepatosplenic T-cell lymphoma (HSTCL) in patients with inflammatory bowel disease. Physicians using this drug should be very familiar with this risk as well as with the mutagenic potential to both men and women and with possible hematologic toxicities. Physicians should inform patients of the risk of malignancy with IMURAN. See WARNINGS.
Black Box Warning

- Hepatosplenic T-cell lymphoma – median survival 10 mo.
  - More cases with using AZA and TNF-α inhibitors concomitantly for IBD esp Crohn’s, cases with AZA alone were generally with >3 years of tx (median duration 6 years, range of 2–17 y)
  - Also reported with CsA use in transplant patients, few cases in RA patients were with TNF-α inhibitors + MTX
  - No cases when used for skin disorder as a primary indication – so how much concern should we have?

Other Adverse Effects

- GI side effects (mild nausea, diarrhea, discomfort) most common – can divide doses, take with food
- Secondary infection
- Other malignancy – squamous cell carcinoma
- Pancreatitis – more often when given for GI disorders/IBD
- Cases of Sweet’s syndrome reported
Pharmacogenomics – Still more to Learn!

• Severe refractory cases of pemphigus and pemphigoid had increases in TPMT activity during therapy

• 12 children with AD with repeat measurements of TPMT activity
  - 9 responders with stable levels
  - 2 responders had decreasing TPMT activity, correlating with additional clinical improvement. One case with increasing activity, correlating with poor control.

• Changes in TPMT activity can occur after therapy begins and appear to inversely relate to azathioprine efficacy
  - May consider repeat assessment if not responding or change in response to therapy

### Table 2. Characteristics, Laboratory Test Values, and Optimal 6-TGN Levels for 12 Patients Who Achieved Remission

<table>
<thead>
<tr>
<th>Patient No./Sex/ Age, y</th>
<th>Disease (Lesion Location)</th>
<th>Optimal 6-TGN, pmol/l x 10^12 RBCs</th>
<th>Total 6-TGN, pmol/l x 10^12 RBCs</th>
<th>6-MMP, pmol/l x 10^12 RBCs</th>
<th>TPMT, U/ml of RBCs</th>
<th>Prednisone Dosage, mg/d</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean (Range)</td>
<td>Mean (Range)</td>
<td>Mean (Range)</td>
<td>No.</td>
<td></td>
</tr>
<tr>
<td>1/W/80</td>
<td>BP (gen)</td>
<td>399.8 (279.0-457.0)</td>
<td>350.3 (185.0-457.0)</td>
<td>14.0 (7.0-21.0)</td>
<td>14</td>
<td>12 (8.2-24.0)</td>
</tr>
<tr>
<td>2/F/79</td>
<td>PV (gen)</td>
<td>241.6 (166.0-425.0)</td>
<td>206.2 (112.0-425.0)</td>
<td>63.0 (10.0-145.0)</td>
<td>9</td>
<td>ND</td>
</tr>
<tr>
<td>3/J/54</td>
<td>PF (face)</td>
<td>141.0</td>
<td>86.7 (63.0-141.0)</td>
<td>536.4 (0.0-13.092)</td>
<td>7</td>
<td>21.9 (16.7-25.0)</td>
</tr>
<tr>
<td>4/F/55</td>
<td>PV (oral, genital)</td>
<td>269.6 (149.0-321.0)</td>
<td>219.9 (62.0-221.0)</td>
<td>513.9 (71.9-24.0)</td>
<td>15</td>
<td>17.4 (12.3-23.0)</td>
</tr>
<tr>
<td>6/W/68</td>
<td>BP (gen)</td>
<td>143.5 (82.0-219.0)</td>
<td>147.9 (82.0-219.0)</td>
<td>162.0 (43.0-84.5)</td>
<td>11</td>
<td>21.9 (18.1-27.0)</td>
</tr>
<tr>
<td>7/F/43</td>
<td>PV (oral, chest)</td>
<td>74.4 (49.0-137.0)</td>
<td>75.3 (49.0-83.0)</td>
<td>649.4 (0.1-168.0)</td>
<td>5</td>
<td>ND</td>
</tr>
<tr>
<td>8/F/42</td>
<td>PV (oral)</td>
<td>101.6 (48.0-129.0)</td>
<td>84.1 (48.0-129.0)</td>
<td>588.0 (243.0-345.0)</td>
<td>6</td>
<td>ND</td>
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<tr>
<td>9/F/90</td>
<td>BP (oral)</td>
<td>230.0 (207.0-253.0)</td>
<td>230.0 (207.0-253.0)</td>
<td>2490.0 (314.0-337.0)</td>
<td>7</td>
<td>ND</td>
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<tr>
<td>11/J/67</td>
<td>BP (oral)</td>
<td>142.0 (108.0-138.0)</td>
<td>121.5 (86.2-150.0)</td>
<td>652.2 (231.2-377.0)</td>
<td>7</td>
<td>ND</td>
</tr>
<tr>
<td>12/F/53</td>
<td>PV (oral)</td>
<td>273.6 (196.0-383.0)</td>
<td>273.0 (196.0-383.0)</td>
<td>6911.0 (20.750)</td>
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<tr>
<td>13/M/35</td>
<td>BP (oral)</td>
<td>119.8 (86.0-140.0)</td>
<td>122.0 (86.0-162.0)</td>
<td>250.0 (668.0-686.0)</td>
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<td>ND</td>
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<tr>
<td>14/M/62</td>
<td>PV (oral)</td>
<td>101.3 (83.0-124.0)</td>
<td>111.0 (83.0-137.0)</td>
<td>387.0 (815.0-835.0)</td>
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<td>ND</td>
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</tbody>
</table>

Abbreviations: BP, bullous pemphigoid; gen, generalized; HM, homoezygote, wild type; HZ, heterozygote; 6-MMP, 6-mox PCR, polymerase chain reaction; PF, pemphigus foliaceus; PV, pemphigus vulgaris; RBCs, red blood cells; 6-TGN, 6-thio inductors of TPMT activity during treatment with azathioprine, calculated as the difference between the highest and the lowest dose of TPMT activity.

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### Table 3. Characteristics and Laboratory Test Values for Patients Not Included in the Calculation of Optimal 6-TGN

<table>
<thead>
<tr>
<th>Patient No./Sex/ Age, y</th>
<th>Disease (Lesion Location)</th>
<th>Optimal 6-TGN, pmol/l x 10^12 RBCs</th>
<th>Total 6-TGN, pmol/l x 10^12 RBCs</th>
<th>6-MMP, pmol/l x 10^12 RBCs</th>
<th>TPMT, U/ml of RBCs</th>
<th>TPMT PCR Genotyping</th>
<th>Comments</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Mean (Range)</td>
<td>Mean (Range)</td>
<td>Mean (Range)</td>
<td>No.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4/F/50</td>
<td>PV (gen)</td>
<td>NA</td>
<td>NA</td>
<td>5 (24.9-30.7)</td>
<td>6.5</td>
<td>HM</td>
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<tr>
<td>10/F/59</td>
<td>BP (loc)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>15/F/56</td>
<td>PV (oral)</td>
<td>159.3 (130.0-207.0)</td>
<td>159.3 (130.0-207.0)</td>
<td>379.0 (377.0-298.0)</td>
<td>14.3</td>
<td>ND</td>
<td></td>
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<tr>
<td>16/F/61</td>
<td>PV (oral)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>17/F/14</td>
<td>PV (oral)</td>
<td>174.0</td>
<td>174.0</td>
<td>53.0</td>
<td>1.0</td>
<td>ND</td>
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<tr>
<td>18/M/67</td>
<td>PV (oral)</td>
<td>127.0</td>
<td>127.0</td>
<td>67.0</td>
<td>1.7</td>
<td>ND</td>
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<tr>
<td>19/M/90</td>
<td>PV (oral)</td>
<td>155.2 (45.0-301.0)</td>
<td>59.0 (261.0-10)</td>
<td>25.7 (18.9-36.4)</td>
<td>17.6</td>
<td>HM</td>
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<tr>
<td>20/F/77</td>
<td>PV (oral)</td>
<td>82.8 (41.0-137.0)</td>
<td>219.0 (11-653.0)</td>
<td>26.7 (20.4-42.3)</td>
<td>23.6</td>
<td>HM</td>
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<tr>
<td>21/F/82</td>
<td>PV (oral)</td>
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<td>NA</td>
<td>18 (13.7-22.8)</td>
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<tr>
<td>22/F/50</td>
<td>PV (oral/cheek)</td>
<td>76.2 (23.0-137.0)</td>
<td>176.0 (314.0-182.0)</td>
<td>13.4 (7.7-28.5)</td>
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<tr>
<td>23/M/32</td>
<td>PV (oral)</td>
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<td>NA</td>
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<tr>
<td>24/F/43</td>
<td>PV (oral)</td>
<td>245.7 (97.0-358.0)</td>
<td>378.0 (314.0-182.0)</td>
<td>21.8 (17.8-27.7)</td>
<td>9.9</td>
<td>HM</td>
<td></td>
</tr>
<tr>
<td>25/M/60</td>
<td>PV (oral)</td>
<td>50.5 (10.0-79.0)</td>
<td>19.0 (147.0)</td>
<td>9.3 (21.5-94.7)</td>
<td>11.5</td>
<td>HM</td>
<td></td>
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<tr>
<td>26/F/48</td>
<td>PV (oral)</td>
<td>266.7 (118.0-374.0)</td>
<td>2043.0 (227.0-5260)</td>
<td>23.2 (15.7-24.7)</td>
<td>ND</td>
<td></td>
<td></td>
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<tr>
<td>27/F/48</td>
<td>PV (oral)</td>
<td>418.3 (10.0-712.0)</td>
<td>34.0 (547.0)</td>
<td>6.7 (10.9-15.8)</td>
<td>4.9</td>
<td>HM</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AZA, azathioprine; BP, bullous pemphigoid; gen, generalized; GI, gastrointestinal; HM, homoezygote, wild type; HZ, heterozygote; IVIG, intravenous immunoglobulin; LFT, liver function test; loc, localized; 6-MMP, 6-methylmercaptopurine; NA, not applicable; ND, not done; PCR, polymerase chain reaction; PV, pemphigus vulgaris; RBCs, red blood cells; SJ/JS, Steven-Johnson syndrome; 6-TGN, 6-thioguanine nucleotide; TPMT, thiopurine methyltransferase.

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