Systemic Medications for the Dermatology Toolbox: Azathioprine

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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
  - 6-mercaptopurine analog that inhibits purine synthesis – lymphocytes rely on de novo synthesis and more selectively affected
  - 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

- 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
- Monitoring
  - Baseline: CBC, renal and liver function, TB testing, hepatitis B and C, HIV
  - Follow-Up: CBC, renal and liver function at 2-4 weeks then monthly x 2-3 months then Q 2-3 months; repeat infectious tests annually
### Contraindications

- Demonstrated hypersensitivity to azathioprine
  - 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
  - Dose reduction needed with allopurinol
  - May have higher risk of cytopenia with aminosalicylates, cotrimoxazole, ACE inhibitors, ribavirin
  - Can inhibit warfarin effect

### Black Box Warning

- Hepatosplenic T-cell lymphoma – median survival 10 months
  - 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

### Still more to learn about pharmacogenomics!

- Severe refractory cases of pemphigus and pemphigoid had increases in TPMT activity during therapy
  - 12 children with AD with repeat measurements of TPMT activity
    - Nine responders with stable levels
    - Two responders had decreasing TMPT 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

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Thai and Pindelli, J Crohns Colitis, 2010;4:511-22.