Systemic Medications for the Dermatology Toolbox: Azathioprine

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DISCLOSURE OF RELATIONSHIPS WITH INDUSTRY

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DISCLOSURES

No relevant conflict of interest
Will discuss off label use of medication
Azathioprine uses

- FDA approved for rheumatoid arthritis and prevention of renal transplant rejection
- In dermatology:
  - Immunobullous disease
  - Atopic dermatosis and eczematous disease
  - Photodermatoses
  - Other recalcitrant diseases: connective tissue disease, vasculitis, psoriasis, lichen planus, prurigo nodularis, Behcet’s disease, GVHD, etc.
Pharmacokinetics

- Nearly completely absorbed by GI tract and metabolized in liver and RBCs with only 2% excreted unchanged in the urine
- Does not cross blood brain barrier but does cross the placenta
- Peak plasma levels in less than 2 hours, half-life of 5 hours
- Mechanism of action:
  - 6-mercaptopurine analog that inhibits purine synthesis (more selectively affects lymphocytes as they rely on de novo synthesis)
  - Blocks the CD 28 costimulatory signal affecting T cell activation
- 6-thioguanine the active metabolite slowly accumulates in tissues and provides maximal clinical immunosuppression around 8-12 weeks, initial improvement after at least 6-8 weeks
Thiopurine metabolism

Products anabolized to active toxic purine analogs (6-thioguanine nucleotides and metabolites) that mediate principal effects

Some active metabolites (thio-inosinic acid) renally eliminated
Azathioprine prescribing

- 50 mg scored tablet
- Usual dosing: 2.5 mg/kg/day, depends on TPMT activity
- Monitoring:
  - History and PE, medication review at start
  - Baseline: TMPT phenotype testing, CBC, CMP, hepatitis, TB testing, HIV, UPT
  - Follow up: CBC, LFTs in 2 weeks and 4 weeks after first dose or dose change, then CBC and CMP every 2 months, repeat infectious panel annually
TMPT genetic polymorphisms affect bone marrow suppression risk

- 1 in 300 individuals has undetectable TPMT, 10% have low activity
  - Low activity correlates with higher risk of suppression

- Red blood cell TPMT activity to guide dosing
  - Normal/high: 2.5 mg/kg/day, increase by 0.5 mg/kg/day as needed
  - Intermediate: 1 mg/kg/day, increase by 0.25 mg/kg/day as needed
  - Low: do not use

- TPMT activity can change after starting azathioprine and should be rechecked if clinical response decreases

- Cessation should strongly be considered if the following cytopenias
  - WBC < 3500-4000/mm3, Hg < 10g/dl, and Platelets < 100,000/mm3

Contraindications

- Hypersensitivity to azathioprine (rare)
  - Fever, nausea, vomiting, diarrhea, arthralgias, malaise, myalgias, transaminitis, rash, and possibly respiratory distress, renal insufficiency, hypotension/shock, usually in first month of therapy, more commonly if on methotrexate or cyclosporine

- Very low or absent TPMT

- Active serious infection

- Pregnancy category D (risk to human fetus but benefit from use may be acceptable despite risks)
  - Levels shows to cross placenta in low concentrations and appear in fetal plasma, mostly inactive metabolism seen due to fetal liver lacking enzyme necessary to convert 6-MP to active metabolites
  - Minimal concentrations in breast milk but theoretical risk of carcinogenesis and immunosuppression outweigh potential benefit of nursing
Drug interactions

- Lower azathioprine dose if taking allopurinol - hematological complications 4-6 weeks after taking together
- Azathioprine induces warfarin resistance - dose-dependent and need to increase warfarin by 3-4 times
- Cytopenias can be seen with cotrimoxazole, ribavirin, ace inhibitors, aminosalicylates
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 months
  - More cases with using TNF-α inhibitors and azathioprine concomitantly for IBD, cases with azathioprine alone were with >3 years of tx (median duration 6 years, range of 2-17 years)
  - Also reported with cyclosporine use in transplant patients, few cases in RA patients were with TNF-α inhibitors and methotrexate
  - No cases when used for skin disorder as a primary indication

Other adverse effects

- Gastrointestinal most commonly - nausea, diarrhea, discomfort seen within first 10 days - can decrease the dose, divide doses or give with food to improve
- Fatigue and malaise after a few weeks - can reduce dose
- Myelosuppression or hepatotoxicity
- Infections
- Other malignancy: squamous cell carcinoma
- Pancreatitis reported in pts with GI disorders primarily
- Febrile neutrophilic dermatosis reported
Azathioprine is an immunosuppressive primarily used for immunobullous diseases, eczematous eruptions, photodermatoses and other uses in dermatology

6-thioguanine is the primary active metabolite

TMPT activity should be checked before starting the medication to decide on dosing

Lab monitoring focus should be on myelosuppression and hepatoxicity

Azathioprine hypersensitivity is a rare but serious complication