Clinical Pharmacology & Toxicology Pearl of the Week

Pharmacogenomics and Immune Reactions

- ✓ HLAs are proteins on antigen presenting cells responsible for presenting immunogenic proteins and substances, or haptens, to T-cells
- ✓ Mutations in HLA genes can increase an individual's risk for severe immune reactions to drugs, including severe cutaneous adverse reactions (SCARs) (ex: DRESS, Steven-Johnson-Syndrome (SJS))
- ✓ Impaired clearance of drugs can also increase an individual's risk for severe immune reactions.

Case

- ✓ A 48 y/o male presents to the emergency department with severe right knee pain, with swelling and erythema. He is admitted to the internal medicine ward, where he is diagnosed as having an acute gout flair.
- ✓ The patient is started on naproxen, colchicine, prednisone and a PPI. Once the flair is settled, the plan is to begin allopurinol therapy, along with non-pharmacologic management of gout.
- ✓ You had recently read about HLA-B*58:01 testing, and order it through Alberta Precision Labs.
- ✓ How will the result affect your management in this patient?

What factors increase a patient's risk for a hypersensitivity (immune) reaction?

- ✓ Hypersensitivity reactions can be difficult to predict, and have multiple factors that contribute to their pathogenesis
  - Genetic variants in HLA proteins can increase the risk of hypersensitivity reactions
  - Previous Epstein-Barr Virus, Human Herpes Virus 6 or 7, or cytomegalovirus infection
  - Increased metabolism to more immunogenic metabolites, or decreased clearance of these metabolites (see Pharmacogenomics and Drug Metabolism)
    - Increasing the patient exposure to the immunogenic compounds
  - Underlying immunogenicity of the drug
- ✓ Unfortunately, the presence or absence of any of these factors cannot predict the occurrence of a hypersensitivity reaction. They only influence the underlying risk.

Examples of Clinical Applications

- ✓ **Allopurinol**
  - HLA-B*58:01 genotype is associated with 34-580x increased risk for SCARs.
  - HLA-B*58:01 genotype is more common in Asian and Asia-Pacific populations.
  - HLA-B*58:01 genotype is an absolute contraindication to allopurinol therapy. Recommendations are to use alternative uric acid lowering pharmacologic and non-pharmacologic therapies.
  - Additional considerations increasing the risk of SCARs in all populations:
    - Higher allopurinol doses
    - Concurrent diuretic use (decreases clearance of allopurinol)
    - Concurrent antibiotic use (decreases clearance of allopurinol)
    - Chronic Kidney Disease (decreases clearance of allopurinol)
- ✓ **Aromatic Anti-epileptics**
  - HLA-B*15:02 genotype is associated with increased risk for SCARs for patients exposed to carbamazepine, oxcarbazepine, phenytoin and fosphenytoin.
  - HLA-A*31:01 genotype is associated with increased risk for SCARs for patients exposed to carbamazepine and oxcarbazepine.
  - HLA-B*15:02 and HLA-A*31:01 genotypes are more common in Asia-Pacific and South-East Asian populations. HLA-A*31:01 is common in northern European populations, up to 5%.
  - Strong recommendations to avoid **carbamazepine and oxcarbazepine** for patients with HLA-B*15:02 or HLA-A*31:01 genotypes due to increased risk of SCARs. Recommendation to use other anti-epileptics.
  - Strong recommendations to avoid phenytoin and fosphenytoin for patients with HLA-B*15:02 genotype due to increased risk for SCARs. Recommendation to use other anti-epileptics.

- The risk of cross-reactivity with other aromatic anti-epileptics (Ex: lamotrigine, phenobarbital) is unknown, but use of any aromatic anti-epileptics in patients with HLA-B*15:02 and HLA-A*31:01 should be approached with caution.

✓ **Abacavir**
- HLA-B*57:01 genotype is associated with increased risk for SCARs.
- HLA-B*57:01 genotype are found in 7% of Caucasian and up to 20% of South-West Asian populations.
- HLA-B*57:01 genotype is a contraindication to abacabir therapy. Recommendations are to select an alternative anti-retroviral agent.

Case Resolution

✓ You receive the results that the patient is negative for the HLA-B*58:01 mutation.
- He does not have an absolute contraindication to allopurinol

✓ However, a negative HLA-B*58:01 mutation does not mean he cannot have a SCAR. You minimize the risk through the following actions:
- Insure he has appropriate renal function to clear allopurinol
- Insure he doesn't have significant drug-drug interactions (ex: diuretic or antibiotic use)
- Begin with a low dose of allopurinol, and titrate based off of serum uric acid levels until the target is reached (100 mg PO daily, titrated up every 2-4 weeks until uric acid <0.36 mmol/L)
- Advise the patient on the risk of SCARs, and what signs or symptoms to watch out for.

✓ Additionally, you advise on non-pharmacologic management including weight loss, exercise, and avoidance of alcohol and purine rich foods.

Consider HLA testing through Alberta Precision Labs prior to prescribing any of the above pharmaceuticals.

The Calgary Clinical Pharmacology physician consultation service is available Mon-Fri, 9am-5pm. The on-call physician is listed in ROCA. Click HERE for clinical issues the CP service can assist with.

The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414, and select option 1.

References:

1. Brunton L, Hilal-Dandan R, Knollmann B, editors. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 13th ed. New York: McGraw Hill Medical; c2018
2. Peck RW. Precision Medicine Is Not Just Genomics: The Right Dose for Every Patient. Annu Rev Pharmacol Toxicol. 2018;58:105-122. doi:10.1146/annurev-pharmtox-010617-052446
3. https://cpicpgx.org/guidelines/
4. Day RO, Graham GG, Hicks M, McLachlan AJ, Stocker SL, Williams KM. Clinical pharmacokinetics and pharmacodynamics of allopurinol and oxypurinol. Clin Pharmacokinet. 2007;46(8):623-644. doi:10.2165/00003088-200746080-00001