The Future of Pharmacogenetics in HIV Clinical Care

A Genetic Test to Screen for Abacavir Hypersensitivity Reactions

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Objectives

- Introduce the concept of pharmacogenetics in predicting therapeutic response and toxicity
- Review the role of Abacavir (ABC) in HIV care
- Review ABC Hypersensitivity Reactions
- Discuss new genetic test to predict and prevent ABC Hypersensitivity
- Discuss other pharmacogenetic research in HIV
- RN’s perspective on the test for ABC hypersensitivity
How Come People Respond Differently to the Same Medications?

Meds effective

Meds not effective

Few side-effects

Lots of side-effects
Factors That Effect Medication Response

- **Adherence**
  *if, when and how one takes meds*

- **Food**
  *Increase or decrease absorption*

**Concurrent medications**
*can block absorption, increase or decrease metabolism*

- **Concurrent medical conditions**
  *eg. kidney and liver disease effect metabolism and elimination*

- **Genetics**
  *metabolizing enzymes, cellular transport genes, HLA immune response genes*

- **Race**

- **Gender**

- **Other factors**
  *pregnancy, age, body weight*
Pharmacogenetics
interaction between meds and genes

- **Definition**
  - the study of how people differ genetically in their dose-response and/or toxicity to different drugs

- **Application**
  - to develop tests that predict side effects and Rx effect to individualize therapy

- **Goal**
  - to find the right drug, at the right dose, for the right person
Potential of pharmacogenetics

1. People who respond poorly with lots of side effects
   Treat with alternative drug or dose

2. People who respond well with few side effects
   Treat with conventional drug or dose

Dr. Elizabeth Phillips
Pharmacogenetic Studies in HIV

- Metabolism of nevirapine, efavirenz and PIs
- To predict peripheral neuropathy, lipodystrophy and lipid disorders
- Hyperbilirubinemia with atazanavir
- Hypersensitivity to nevirapine, septran, amprenavir, T-20, efavirenz and abacavir
- Prediction of abacavir hypersensitivity is closest to being used in HIV care
Abacavir
Nucleoside Reverse Transcriptase Inhibitor (NRTI)

Abacavir 300mg
Abacavir 600mg
3TC 300mg
AZT 300mg

Abacavir 300mg
Abacavir 600mg
3TC 300mg
AZT 300mg

GX 623
"KIVEXA"
GX LL1
ZIAGEN
TRIZIVIR
Use of Abacavir in PHA care

- Longstanding Nucleoside Reverse Transcriptase Inhibitor (NRTI)
- Approved for use in 1998
- Commonly used first line agent (DDHS, IAS-US, BCCFE Rx guidelines)
- Commonly used in treatment simplification
- Studied to reduce lipodystrophy
- Studied to reduce lipid disorders
BC Centre for Excellence in HIV/AIDS recommended first line therapy

- 2 nucleoside (or nucleotide) reverse transcriptase inhibitors
  \((N[Nt]RTIs)\)*
  plus either:
- a non-nucleoside reverse transcriptase inhibitor (NNRTI)
- a ritonavir-boosted protease inhibitor (PI/r)

*Recommended N[Nt]RTI Backbones: Lamivudine (3TC) & Abacavir (ABC), Zidovudine (AZT) & Lamivudine (3TC), Tenofovir (TDF) & Emtricitabine (FTC)
N = 770 antiretroviral-naive patients randomized to
3TC + EFV + ABC once daily (n = 384) vs
3TC + EFV + ABC twice daily (n = 386)
Similar efficacy and safety at Week 48
Grade 3/4 hypersensitivity reaction: 5% with once daily, 2% with twice daily ($P = .02$)

Lipodystrophy Reduction (MITOX)
Limb Fat Change After Switch From d4T or ZDV to ABC

*Comparison with baseline values.

Hyperlipidemia Management (NEFA)
Metabolic Effects of Switch From PI to ABC, NVP, or EFV:

NEFA substudy: n = 29 switched to ABC, n = 32 switched to EFV, n = 29 switched to NVP

Abacavir Hypersensitivity Reaction (HSR)

- Allergic reaction to Abacavir
- Rash, fever, respiratory (breathing) and GI (gut) symptoms
- 5.4% of all patients
- Higher in caucasians ~8%
- 2-3% “false-positive” rate
- Symptoms start within 6 weeks of taking Abacavir (in 90% of cases)
- Symptoms resolve on discontinuation
- Symptoms worsen on rechallenge
- Small rate of mortality on rechallenge
Abacavir HSR Symptoms

- Fever
- Rash
- GI symptoms
  - diarrhea
  - nausea
  - vomiting
  - stomach pain
- Flu like symptoms
  - muscle aches
  - fatigue
- Respiratory symptoms
  - cough
  - sore throat
  - shortness of breath
Drug Rash with eosinophilia and systemic syndrome DRESS, due to abacavir
Research Diagnosis of HSR

- Onset of ≥ 2 symptoms of fever, rash, GI symptoms, lethargy, joint pain, muscle pain, respiratory symptoms
- Start < 6 weeks after starting Abacavir
- Gets better within 72 hours of stopping Abacavir
- No alternative explanation
- Patch test can confirm diagnosis
ABACAVIR POSITIVE PATCH:
Concentration Response

OPEN PATCH

CLOSED PATCH

Dr. Elizabeth Phillips
Abacavir HSR Symptoms

- Hard to diagnose
- Many “false-positive” diagnoses because symptoms are non-specific
- Symptoms overlap with viral illnesses and other drug allergies (e.g., amprenavir, septra, T-20, nevirapine)
- Can lead to over-diagnosis and people being taken off abacavir unnecessarily
“Costs” of Overdiagnosing Abacavir HSR

Major reason for stopping abacavir early (< 6 weeks) is concern about HSR

British Columbia Data (1998-2004):

171/1448 (12%) on abacavir discontinued early

Stopping early associated with significantly longer time to undetectable VL ~131 vs. 81 days for patients tolerating ABC, p<.001

Patients stopping early more likely to seek care from emergency physicians or specialists ~ higher costs for services within first 60 days of starting abacavir

Phillips E, Antiviral Therapy 2005;10:L60
Abacavir HSR Now Known to be Associated with a Specific Gene

HLA-B*5701
What the “H” is HLA?

• HLA stands for Human Leukocyte Antigens
• A classification system of on chromosome 6 that “code” proteins on the surface of white blood cells involved in immune response
• HLA is a tissue typing system similar to the “ABO” blood typing system
• Used to help predict transplant compatibility, autoimmune diseases (eg lupus, some forms of arthritis), and some side effects
Blood Cell Antigen Systems

Blood Cells

Chromosome 6

Chromosome 9

Human Leukocyte Antigen (HLA) System

♦ Transplant compatibility
♦ Association with autoimmune diseases
♦ Prediction of some drug adverse effects

ABO-Rh Blood Typing System

♦ Transfusion compatibility
HLA-B*5701 and Abacavir HSR

- ABC HSR seemed to run in families and with varying frequencies in ethnic groups.
- Mallal (Australia) & Hetherington (England) first reported association of HLA-B*5701 gene and ABC HSR.
- Phillips (Canada) reported 27/27 patch test positive patients were HLA-B*5701 positive.
- Small studies have shown that using HLA-B*5701 screen test decreases the incidence of ABC-HSR (large study in Europe and Australia ~PREDICT-1~ will try and confirm).
- Research being done in different ethnic groups (SHAPE study).
HLA-B*5701 in Different Populations

- **W. EUROPE**: 5-7%
- **UK**: ~8%
- **INDIA**: 5-20% (NB 2.5% N.E. provinces)
- **JAPAN**: 0%
- **CHINA**: 0% (NB 2.5% N.E. provinces)
- **MIDDLE EAST**: 1-2% (NB 5-7% Ashkenazi Jews)
- **THAILAND**: 4-10%* (Urban Bangkok 3.6%, Thai Dai Lue (NE Thai) ~11%, Southern Thai Muslim 3%)
- **AUSTRALIA**: ~8%
- **US Caucasian**: ~8%
- **US Asian**: ~1%
- **US African-American**: ~2.5%
- **US Hispanic**: ~2%
- **S. AMERICAN**: 5-7%
- **Subsaharan AFRICA**: <1%
- **MEDITERRANEAN**: 1-2%
- **S. AMERICAN**: Caucasian 5-7%

*THAILAND B*57 carriage:
- Urban Bangkok 3.6%
- Thai Dai Lue (NE Thai) ~11%
- Southern Thai Muslim 3%

Nolan et al, J HIV Ther 2003; 8(2):36-41
How Well Does HLA-B*5701 Predict Abacavir HSR?

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<th></th>
<th>Mallal et al(^{[14]})</th>
<th>GlaxoSmithKline(^{[9]})</th>
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<td>White</td>
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<tr>
<td>Cases/controls</td>
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<td>48%</td>
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<tr>
<td>Negative predictive value</td>
<td>98%</td>
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HLA-B*5701 Testing in Canada

- Research studies in 7 centres
- Sites receive training in diagnosis of HSR & HLA-B*5701 test technology
- Only for people who have never taken ABC
- Blood collection in 1 lavender-top tube
- ~ 1-3 week turn-around for results
- Negative Result = relatively low risk of developing HSR
- Positive Result = higher risk of developing HSR and Abacavir should be avoided
- Dr. Richard Harrigan is doing the testing at BCCFE along with other HLA screening
HLA-B*5701 Testing in the Clinic

- More research to be done, especially in populations with low frequency of HLA-B*5701.
- Improvements in technology will bring the cost of the test down.
- Not to be used as a confirmatory test of HSR.
- Not to be used as a justification for restarting Abacavir.
- Can never replace clinical assessment and judgement.
HLA-B*5701 Testing in the Clinic

~potential problems~

- Will work better in populations with higher frequency of HSR and less racial intermarriage
- There is the concern doctors might rely too much on the test and ignore symptoms
- Cost
- Laboratory procedures need to be standardized
Other Potential Pharmacogenetic Applications

- **Drug Metabolizing Enzymes**
  - CYP3A5 ~ Indinavir, Saquinavir
  - CYP2C19 ~ Nelfinavir
  - CYP286 ~ Efavirenz, Nevirapine
  - UGT1A1 ~ Atazanavir

- **Drug Transporters**
  - OATs ~ Tenofovir
  - MRPs ~ PIs, NRTIs
  - P-gp ~ PIs, Efavirenz

- **Immune Response Genes**
  - HLA-DRB1*0101 ~ Nevirapine
  - HLA-B*5701 ~ Abacavir
The Future of Pharmacogenetics in HIV Care

- Better individualization of therapy through prediction of therapeutic response and side effects
- Currently still a research tool
- Closest to “standard of care’’ is HLA testing for Abacavir HSR
- No test or technology will replace clinical judgement
Testing for Abacavir Hypersensitivity
RN’s Perspective

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