Genetically-Mediated Serious Skin Rash
Singapore Health Sciences Authority Experience

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Vigilance, Compliance and Enforcement Branch
Health Products Regulation Group
Health Sciences Authority

For the HSA Pharmacogenetics Team
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Singapore and Washington DC

Land Area - 277 sq mi.
Singapore Demographics

- Population – 5.47 million (June 2014)
  - 3.87 million citizens and permanent residents
  - 1.6 million foreign workers and other non-residents

- Ethnic composition of citizens & PRs

- Chinese: 74.2%
- Malays: 13.3%
- Indians: 9.1%
- Other: 3.3%
Health Sciences Authority

- HSA Board
- Chief Executive Officer
- Internal Audit & Risk Management

**Corporate Services Group**
- Departments
  - Corporate Communications
  - Emergency Planning
  - Facilities Management
  - Finance
  - Human Capital Management and Learning & Development
  - Information Management
  - Legal & Prosecution
  - Organisation Development & Excellence
  - Strategy & Business Transformation

**Health Products Regulation Group**
- Divisions
  - Pre-marketing
  - Vigilance, Compliance & Enforcement
  - Audit & Licensing

**Blood Services Group**
- Branches
  - Blood Resources
  - Blood Supply
  - Patient Services
  - Clinical Services

**Applied Sciences Group**
- Divisions
  - Forensic Medicine
  - Forensic Science
  - Illicit Drugs
  - Analytical Toxicology
  - Biology
  - Pharmaceutical
  - Food Safety
  - Chemical Metrology
## Prevalence of Skin Related ADRs in Singapore

**Top 10 System Organ Class/ Body system disorder (1/1/2014 to 12/31/2014)**

<table>
<thead>
<tr>
<th>No.</th>
<th>System organ class</th>
<th>No. of reports</th>
<th>% of total no. of ADR terms quoted</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Skin And Appendages Disorders</td>
<td>12,228</td>
<td>52.3</td>
</tr>
<tr>
<td>2</td>
<td>Body As A Whole - General Disorders</td>
<td>4,192</td>
<td>17.9</td>
</tr>
<tr>
<td>3</td>
<td>Respiratory System Disorders</td>
<td>1,459</td>
<td>6.2</td>
</tr>
<tr>
<td>4</td>
<td>Centr &amp; Periph Nervous System Disorders</td>
<td>1,220</td>
<td>5.2</td>
</tr>
<tr>
<td>5</td>
<td>Gastrointestinal System Disorders</td>
<td>1,213</td>
<td>5.2</td>
</tr>
<tr>
<td>6</td>
<td>Urinary System Disorders</td>
<td>825</td>
<td>3.5</td>
</tr>
<tr>
<td>7</td>
<td>Musculo-Skeletal System Disorders</td>
<td>312</td>
<td>1.3</td>
</tr>
<tr>
<td>8</td>
<td>Vascular (Extracardiac) Disorders</td>
<td>310</td>
<td>1.3</td>
</tr>
<tr>
<td>9</td>
<td>Heart rate and Rhythm Disorders</td>
<td>252</td>
<td>1.1</td>
</tr>
<tr>
<td>10</td>
<td>Metabolic And Nutritional Disorders</td>
<td>219</td>
<td>0.9</td>
</tr>
</tbody>
</table>
Pharmacogenetics Initiative at HSA

- Launched in 2008

- Objectives
  - Develop regulatory expertise in pharmacogenetics
  - Establish collaborative network with healthcare professionals and research institutions
  - Build infrastructure to collect & store DNA samples and clinical data of patients experiencing serious ADRs and drug tolerant controls

- Regulatory Outcome
  - Update drug package inserts
  - Make recommendations to healthcare professionals based on local data
## Drug Class (Oct 2014)

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Number of SJS/TEN Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antiepileptics</strong> <em>(CBZ, phenytoin, lamotrigine)</em></td>
<td>20*</td>
</tr>
<tr>
<td><em>1 case of phenytoin / piperacillin &amp; tazobactam</em></td>
<td></td>
</tr>
<tr>
<td><strong>Antibiotics</strong></td>
<td>16</td>
</tr>
<tr>
<td><strong>Allopurinol</strong></td>
<td>7</td>
</tr>
<tr>
<td><strong>Others</strong> <em>(eg. Paracetamol, NSAIDs, COX-2 inhibitors)</em></td>
<td>16</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>59</strong></td>
</tr>
</tbody>
</table>
CBZ - HLA Genotyping in S’pore

As of 27 Feb 2013

<table>
<thead>
<tr>
<th></th>
<th>CBZ Cases (n=13)</th>
<th>Controls (n=26)</th>
<th>Odds Ratio (OR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-B*1502</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>13</td>
<td>3</td>
<td>181 (8.7 to 3785)</td>
</tr>
<tr>
<td>Negative</td>
<td>0</td>
<td>23</td>
<td></td>
</tr>
</tbody>
</table>

Sensitivity = 13/13 = 100%
Specificity = 23/26 = 88.5%

- Data from HSA’s study supports strong association between CBZ-induced SJS/ TEN and HLA-B*1502

(The Pharmacogenomics Journal 2014; 14: 316-321)
CBZ Cost-Effectiveness Study

To Genotype or not to Genotype?

• Population of interest:
  • Newly diagnosed adult epilepsy patients in Singapore for whom CBZ/Phenytoin (PHT) is considered appropriate treatment

• 3 strategies were compared:
  • Status quo: no genotyping and prescribe CBZ/PHT to all new patients as first line treatment
  • Genotype and prescribe CBZ/PHT to those who test negative and valproate for those who test positive
  • No genotyping and prescribe valproate to all patients

Neurology 2012; 79: 1259-1267
## Prevalence of HLA-B*1502

<table>
<thead>
<tr>
<th>Population</th>
<th>Frequency of Carriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Singapore Chinese</td>
<td>1 in 8</td>
</tr>
<tr>
<td>Singapore Malays</td>
<td>1 in 5</td>
</tr>
<tr>
<td>Singapore Indians</td>
<td>1 in 25</td>
</tr>
<tr>
<td>Caucasians</td>
<td>1 in 500</td>
</tr>
<tr>
<td>Japanese</td>
<td>≤1 in 1000</td>
</tr>
</tbody>
</table>

1. Allelefrequencies.net
2. Singapore Immunology Network
A commonly accepted cost-effectiveness threshold:
USD$50,000/QALY ~ SGD65,000/QALY

<table>
<thead>
<tr>
<th>Population</th>
<th>ICER ($S/QALY) when genotyping cost at $205</th>
</tr>
</thead>
<tbody>
<tr>
<td>Singapore population (ethnicity weighted)</td>
<td>S$31,120</td>
</tr>
<tr>
<td>Singapore Chinese</td>
<td>S$38,620</td>
</tr>
<tr>
<td>Singapore Malays</td>
<td>S$8,430</td>
</tr>
<tr>
<td>Singapore Indians</td>
<td>S$123,000</td>
</tr>
</tbody>
</table>

Neurology 2012; 79: 1259-1267
Regulatory Action

End 2012

• Analysed findings from study and consulted with neurologists, psychiatrists, dentists, primary care drs, dermatologists

2013

• MOH and HSA jointly convened an expert panel to formulate local recommendations for HLA-B*1502 testing
• Centralised HLA-B*1502 testing laboratory
• Dear Healthcare Professional Letter, jointly issued by MOH and HSA
• Strengthened package inserts of carbamazepine-containing medicines
• 75% subsidy for genotyping test for low-income patients
Final Recommendations

• Genotyping for the HLA-B*1502 allele prior to the initiation of CBZ in new patients of Asian ancestry is considered the **standard of care** by MOH

• The package insert of CBZ strengthened to **highly recommend** the testing of this genetic variant in this group of patients

• Genotyping is **not required** in patients who have been taking CBZ for \( \geq 3 \) months without adverse reactions
Final Recommendations

• CBZ should not be prescribed before knowing HLA-B*1502 test results

• Treatment alternatives (excluding phenytoin) are recommended for patients who have tested positive for HLA-B*1502

• Preliminary data have shown a suspected association between this genetic marker and phenytoin-induced SJS/TEN, although the effect size is not as large
Final Recommendations

• Some Asian patients positive for HLA-B*1502 and treated with CBZ will not develop SJS/TEN and patients negative for HLA-B*1502 can still develop SJS/TEN

• The role of other factors in the development of SJS/TEN such as drug dose, compliance, concomitant medications, co-morbidities and level of dermatologic monitoring have not been studied

• Genetic testing should not substitute for appropriate clinical vigilance and patient management
CBZ-induced SJS Cases

• 2003 – 2012: 15 cases on avg. per year

• 2013 before making testing std of care: 4 cases

• After making testing std of care: 0 cases
Learning Points

• Importance of engaging multiple stakeholders, especially clinicians, pre- and post-“standard of care” letter
• Importance of lowering cost and turnaround time of genotyping test
• C/E analysis to inform decisions on subsidy for genotyping test
Acknowledgements

- All participating clinicians & coordinators from Sg Gen Hosp, Nat’l Univ Hosp, Changi Gen Hosp
- Singapore Immunology Network, A*STAR
- Duke-NUS Graduate Medical School
- Singapore Biobank/ NUHS Tissue Repository
- Pharmacogenetics Expert Panel
- Pharmacogenetics Team at HSA
Thank you