Clinical and Diagnostic Aspects of Severe Cutaneous Adverse Reactions (SCAR) in the Asia-Pacific Region

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Outline

• Classification of SCAR

• Pathogenesis and application to in-vitro diagnostic tests

• SCAR in special populations in Asia
  - Elderly
  - Acetaminophen
  - Tuberculous drug allergy

• Pharmacogenetic testing: HLA-B*5801 and Allopurinol SCAR in gout
SCAR

- Stevens-Johnson syndrome (SJS)
  - Detachment < 10% BSA + widespread erythematous or purpuric macules or flat atypical targets

- Overlap Stevens-Johnson syndrome-toxic epidermal necrolysis (SJS/TEN)
  - Detachment 10%-30% BSA + widespread purpuric macules or flat atypical targets

- Toxic epidermal necrolysis (TEN)
  - Detachment > 30% BSA

- Acute Generalized Exanthematous Pustulosis (AGEP) *
- Drug reaction, Eosinophilia and Systemic Symptoms (DRESS)*
- Drug Induced Hypersensitivity Syndrome (DiHS) *

Confluent purpuric macules and limited areas of skin detachment in SJS

Detachment of large epidermal sheets in SJS/TEN overlap; atypical target lesions are still present

SJS and TEN part of one disease entity of Severe Cutaenous Adverse Reactions (SCAR) with increasing severity

French LE. Allgol Int 2006; 55:9-16
# SCORTEN

<table>
<thead>
<tr>
<th>Prognostic Factors</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;40 years</td>
<td>1</td>
</tr>
<tr>
<td>Heart rate &gt;120 beats/minute</td>
<td>1</td>
</tr>
<tr>
<td>Cancer or hematologic malignancy</td>
<td>1</td>
</tr>
<tr>
<td>Body surface area involved &gt;10%</td>
<td>1</td>
</tr>
<tr>
<td>Serum urea level &gt;10 mM</td>
<td>1</td>
</tr>
<tr>
<td>Serum bicarbonate level &gt;20 mM</td>
<td>1</td>
</tr>
<tr>
<td>Serum glucose level &gt;14 mM</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SCORTEN</th>
<th>Mortality Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>3.2</td>
</tr>
<tr>
<td>2</td>
<td>12.1</td>
</tr>
<tr>
<td>3</td>
<td>35.8</td>
</tr>
<tr>
<td>4</td>
<td>58.3</td>
</tr>
<tr>
<td>5</td>
<td>90</td>
</tr>
</tbody>
</table>
Definitive and probable diagnoses: Confirmed overlap SCARs

Overlaps between AGEP, DRESS, SJS-TEN are uncommon.

Severe cutaneous adverse reaction (SCAR) groups in the world

Drug hypersensitivity meeting (EACCI)

EuroSCAR/RegiSCAR

Japan SCAR/Asian SCAR

SEA-SCAR (Malaysia, Singapore, Philippine, Thailand, Taiwan)

T-SCAR

Courtesy of Hung SI, NIH SJS/TEN Workshop, Mar 2015
Pathogenesis

Drug antigen presentation
1. the hapten/prohapten theory
2. the p-i concept
3. the altered peptide repertoire

Genetic polymorphism in HLA or drug metabolizing enzymes
- HLA-B*15:02 for CBZ-induced SCAR
- HLA-B*58:01 for allopurinol-induced SCAR
- CYP2C9*3 for phenytoin-induced SCAR

Severe cutaneous adverse drug reactions (SCAR)

Immune and cell death mechanisms
- Innate and adaptive immunity
- Th1/2 cytokines (e.g., IFN-γ, TNF-α, IL-5 and TARC)
- Cytotoxic proteins (e.g., granulysin, FasL and perforin/granzyme B)
- Cell death signals (e.g., miR-18a-5p and annexin A1)

Environmental or non-genetic factors
- Virus infection (HSV, CVA6, HHV6 and etc.)
- Impaired drug metabolism in CKD

Systems involved in SCAR. Drug antigen presentation, genetic polymorphism in human leukocyte antigen (HLA) or drug metabolizing enzymes, immune/cell death mechanisms and environmental or non-genetic factors are all involved in the pathogenesis of SCAR. CBZ, carbamazepine; CKD, chronic kidney disease; CVA, coxsackievirus; HHV, human herpesvirus; HSV, herpes simplex virus; IFN, interferon; IL, interleukin; TARC, thymus and activation regulated chemokine; Th, T-helper; TNF, tumor necrosis factor.

4 models of the interaction of human leukocyte antigen (HLA), drug and T-cell receptor (TCR)
Diagnostic Tests

- In vitro T-Lymphocyte testing

- Drugs are taken up and presented to T-lymphocytes directly or following prior metabolism (mDrug)

- Drug-specific T-cell activation is detected by
  - ↑ T-cell proliferation (a),
  - ↑ expression of activation markers (b), or
  - ↑ secretion of certain cytokines (c).

Möbs C, Pfützner W. Allergo J Int 2014; 23:164-71
The measurement of OXY100/anti-PD-L1-inducing IFN-γ-releasing cells yields a high diagnostic value in distinguishing between allopurinol-allergic and control subjects.

Beneficial in confirming diagnosis of allopurinol-induced SCARs in patients whose reaction develops while taking multiple drugs.
SCAR in the Elderly

Sources: United Nations, Department of Economic and Social Affairs, Population Division. 2013
World Population Prospects: The 2012 Revision.
http://data.un.org
SCAR in the Elderly

• Increase in chronic diseases

• Median age
  - 50 years in EuroSCAR
  - 48-55 years in DRESS cohorts

• Chronic diseases associated with high risk drugs
  - Carbamazepine, phenytoin: scar epilepsy
  - Allopurinol: gout
  - Oxicams/ NSAIDs: joint pains
  - Sulfonamide antibiotics: infections
  - Strontium ranelate: osteoporosis

Heng YK, Lim YL. Curr Opin Allergy Clin Immunol 2015, 15:300-7
SCAR in the Elderly

• **SCORTEN**
  - Age > 40 years predictive of mortality (validated)
  - EuroSCAR: Age > 70 years higher mortality vs age < 40 years
  - Taiwan study: deceased cohort mean age 66.5 years vs surviving cohort mean age 48.7 years


• Risk of mortality (RegiSCAR)
  - Mortality rate 23% (95% CI 19-27%) at 6 weeks and 34% (95% CI 30-39%) at 1 year
  - Serious comorbidities (severe liver or kidney disorders, recent malignancy) and age influenced mortality beyond 90 days and up to 1 year after onset of reaction

  Heng YK, Lim YL. Curr Opin Allergy Clin Immunol 2015, 15:300-7
SCAR and Acetaminophen

- Japanese ADE Database
  - loxoprofen or acetaminophen SCAR
    - Within 2-3 days
    - Adjusted ROR higher in patients aged 0-19 years


- Korean case series
  - Acetaminophen SCAR
  - 6 adults aged 21-77 yo
  - IL-2Ra levels significantly decreased during the convalescence phase
  - Although acetaminophen is relatively safe, the drug can trigger SJS/TEN in patients with suspected viral infections

  Kim EJ, at al. Asia Pac Allergy 2014; 4:68-72
SCAR and TB Drug Allergy

- Combination drug therapies (2REHZ/4HR) for TB (pulmonary/extrapulmonary)

- Identification of culprit drug by “best guess”
  - No well validated in-vitro tests can give the answer quick enough e.g. INH/RIF specific CD4+ T cells in MPE/DRESS
  - Risk of in-vivo tests i.e. delayed IDT, patch tests in SCAR

- Rechallenge-desensitization contraindicated in SCAR

- Need for 2nd line therapies (without Rifampicin), less effective, longer duration of treatment

Castells MC. Immunol Allergy Clin N Am 2009; 29:585-606
Pharmacogenetic Testing

- Pharmacogenomics in risk stratification of patients at risk for SCAR

- Cost-effectiveness of testing in terms of Quality-Adjusted Life-Year (QALYs) gained
  - USD 50,000 per quality-adjusted life-year (QALY) used in health policy circles as a benchmark for the value of care
  - GBP 20,000-30,000 for National Institute of Clinical Excellence (NICE)

- Carbamazepine HLA-B*1502 testing standard of care in Asia
  - Recent study from Hong Kong questioned the cost-effectiveness
  - USD 85,697 per quality-adjusted life year (QALY) compared with no screening


Novel real-time PCR assay for detection of HLA-B*15:02

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</thead>
<tbody>
<tr>
<td><strong>Time consumption</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimated assay time</td>
<td>240 min</td>
<td>45 min</td>
<td>Approximately 80 min</td>
<td>300 min</td>
<td>110 min and 128 min</td>
</tr>
<tr>
<td>Time for result</td>
<td>35 min (loading on gel)</td>
<td>1 min</td>
<td>Time for ΔΔt calculation or loading on gel N/A</td>
<td>30 min (loading on gel)</td>
<td>0 min</td>
</tr>
<tr>
<td>Total time</td>
<td>275 min</td>
<td>46 min</td>
<td>330 min</td>
<td>238 min</td>
<td></td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimated cost of reaction unit</td>
<td>$6.5 USD</td>
<td>$3.8 USD</td>
<td>$15 USD</td>
<td>$7 USD</td>
<td>$4.7 USD**</td>
</tr>
<tr>
<td><strong>Robustness</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>100%</td>
<td>~100%</td>
<td>N/A</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Lowest limit of detection (DNA concentration)</td>
<td>N/A</td>
<td>N/A</td>
<td>~25 ng/reaction</td>
<td>N/A</td>
<td>0.05 ng/μl (TaqMan Probe) 0.5 ng/μl (for SYBR)</td>
</tr>
<tr>
<td>False positive alleles detected in method</td>
<td>Rare alleles in HLA-B*15 group</td>
<td>Heterozygote of HLA-B<em>15:25 and B</em>15:15</td>
<td>Some (less than 1% frequent) alleles</td>
<td>HLA-B<em>15:31 and rare alleles in HLA-B</em>15 group</td>
<td>Heterozygote of HLA-B<em>18 with any alleles such as HLA-B</em>13:01; 15:13; 15:25; 15:36</td>
</tr>
</tbody>
</table>

SBT: Sequence based-typing; SSO: Sequence-specific oligonucleotide; LAMP: Loop-mediated isothermal amplification; AS-PCR: Allele specific PCR; DDB: Direct dot blot hybridization; NPV: Negative predictive value; N/A: not applicable.
** The cost of reaction unit was calculated by cost of DNA extracted kit, master mixes, oligos primers and fluorescent dyes.

D.V. Nguyen et al. Hum Immunol Aug 2016 - Epub ahead of print
Gout in Asia

- Prevalent in east and south-east Asia, elderly males
- HLA-B*5801 carrier frequency in Asia 6.1% 
- In Thailand, HLA-B*5801 assoc with Allo-SJS/TEN, DRESS and MPE *
- Chronic kidney disease as a comorbidity when eGFR < 30 (↑ risk of Allopurinol SCAR)
- Probenecid and Feboxostat (selective xanthine oxidase inhibitor)

Sukasem C, et al. Front Pharmacol 2016; 7:186 *
HLA-B*5801 Testing and Allopurinol SJS/TEN/DRESS

- Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines (Duke University, Durham)
- Positive predictive value \(\approx 1.5\%\) (Han Chinese, Thai)
- Other genes associated in Europeans and Japanese
- High negative predictive value (> 99%) in patients of Asian descent
- False negative genotyping error
- Does not predict non-SCAR e.g. maculopapular exanthem

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Implications for phenotypic measures</th>
<th>Recommendations for allopurinol</th>
<th>Classification of recommendations(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noncarrier of HLA-B*5801 ((^*X/{*X}))(^b)</td>
<td>Low or reduced risk of allopurinol-induced SCAR</td>
<td>Use allopurinol per standard dosing guidelines</td>
<td>Strong</td>
</tr>
<tr>
<td>Carrier of HLA-B<em>5801 (HLA-B</em>5801/{<em>X},(^b) HLA-B</em>5801/HLA-B*5801)</td>
<td>Significantly increased risk of allopurinol-induced SCAR</td>
<td>Allopurinol is contraindicated</td>
<td>Strong</td>
</tr>
</tbody>
</table>

HLA-B, human leukocyte antigen-B; SCAR, severe cutaneous adverse reaction.

\(^a\)Rating scheme described in [Supplementary Table S4](#) online. \(^b\)HLA-B genotype other than HLA-B*5801 is indicated by {*X}.

Cost-Effectiveness of Allopurinol SJS/TEN B*5801 Screening

- **Thailand**
  - Decision analytical and Markov model to estimate life time costs and outcomes represented as quality adjusted life years (QALYs) gained
  - Hypothetical cohort of 1,000 patients, average age 30 years
  - Model: test characteristics, costs, epidemiologic data for Thailand (literature and a retrospective database analysis)
  - Incremental QALY was 5.89 with an ICER of 156,937.04 THB (USD 5,062) per QALY gained


- **Korea**
  - Decision analytical model over 12 months to compare the cost and outcomes
  - Direct medical costs: from real patients with SCARs from 2 tertiary hospitals
  - 1,178,000 KRW (USD 1,055) per QALY gained

Cost-Effectiveness of Allopurinol SJS/TEN B*5801 Screening (Singapore)

<table>
<thead>
<tr>
<th>Strategy</th>
<th>First-line therapy</th>
<th>Genetic testing</th>
<th>Safety program</th>
</tr>
</thead>
<tbody>
<tr>
<td>ULT</td>
<td>Allopurinol</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>ULT + SP</td>
<td>Allopurinol</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>G→ULT</td>
<td>Allopurinol (for HLA-B<em>5801-negative patients) probenecid (for HLA-B</em>5801-positive patients)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>G→SP</td>
<td>Allopurinol</td>
<td>Yes</td>
<td>Yes (for HLA-B*5801-positive patients only)</td>
</tr>
<tr>
<td>G→ULT→SP</td>
<td>Allopurinol (for HLA-B<em>5801-negative patients) probenecid (for HLA-B</em>5801-positive patients)</td>
<td>Yes</td>
<td>Yes (for HLA-B*5801-positive patients who do not respond to probenecid only)</td>
</tr>
<tr>
<td>No ULT</td>
<td>Treatment of acute flares only</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

G: HLA-B*5801 genetic testing; SP: Safety program; ULT: Urate-lowering therapy.

- Health systems perspective - Singaporean, chronic gout, lifetime, on Allopurinol or Probenecid
- Model - incorporated SJS/TEN & gout treatment outcomes, allele frequencies, drug prices and other medical costs
- **Not cost-effective**: based on CE threshold of US$50,000 per quality-adjusted life year, HLA-B*5801-guided ULT selection or enhanced safety program
- Least preferred strategy: avoidance of Allopurinol → uncontrolled gout → ↓ QALY ↑ costs
- Need for biomarker with ↑ PPV for SJS/TEN, less expensive genetic tests or safety programs, or more effective gout drugs.

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Cost (US$)</th>
<th>Incremental cost (US$)</th>
<th>QALYs</th>
<th>Incremental QALYs</th>
<th>ICER (US$/QALY)</th>
<th>Dominance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard ULT</td>
<td>4131</td>
<td>–</td>
<td>14.9966</td>
<td>–</td>
<td>–</td>
<td>Undominated</td>
</tr>
<tr>
<td>ULT + SP</td>
<td>4194</td>
<td>63</td>
<td>14.9974</td>
<td>0.0008</td>
<td>79,140</td>
<td>Undominated</td>
</tr>
<tr>
<td>G--&gt;SP</td>
<td>4419</td>
<td>225</td>
<td>14.9974</td>
<td>0</td>
<td>–</td>
<td>Dominated</td>
</tr>
<tr>
<td>G--&gt;ULT--&gt;SP</td>
<td>4588</td>
<td>394</td>
<td>15.0020</td>
<td>0.0046</td>
<td>85,630</td>
<td>Undominated</td>
</tr>
<tr>
<td>G--&gt;ULT</td>
<td>5160</td>
<td>572</td>
<td>14.9597</td>
<td>-0.0423</td>
<td>-13,510</td>
<td>Dominated</td>
</tr>
<tr>
<td>No ULT</td>
<td>15,310</td>
<td>10,722</td>
<td>14.1319</td>
<td>-0.8701</td>
<td>-12,320</td>
<td>Dominated</td>
</tr>
</tbody>
</table>

G: HLA-B*5801 genetic testing; ICER: Incremental cost–effectiveness ratio; QALY: Quality-adjusted life year; SP: Safety program; ULT: Urate-lowering therapy.
Conclusion

• SCAR syndromes may overlap
  - Monitoring for progression and systemic symptoms

• Improvement in understanding pathogenesis may facilitate development of novel in-vitro assays with increased precision and safety

• Pharmacogenetic testing for Allopurinol SCAR may not be cost-effective depending on cost of the test and who pays for the test
  - Structured safety program for monitoring without HLA testing?