The ugly: Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis and ART

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SJS / TEN and ARV

Introduction

- Epidemiology
  - Non HIV patients: 2-7 / 1,000,000 / year
  - HIV patients: 100 – 1000-fold increase

- Background facts
  - Difficult to prove systematically
  - Other concomitant drugs may be implicated
  - Up to 50% of HIV patients will develop some sort of skin manifestations to treatment

Yunihastuti E, et al. Asia Pac Allergy 2014; 4: 54-67
# SJS / TEN and ARV Pathophysiology

### Drugs involved
- Any drug can be the potential cause

### Effect
- Direct
- Drug metabolites
- Interaction between drugs

<table>
<thead>
<tr>
<th>Drugs used</th>
<th>No. of cases</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibacterial sulfonamides</td>
<td>68</td>
<td>38.4</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>35</td>
<td>19.8</td>
</tr>
<tr>
<td>Tuberculosis drugs</td>
<td>10</td>
<td>5.6</td>
</tr>
<tr>
<td>Nonsteroidal anti-inflammatory drugs</td>
<td>9</td>
<td>5.1</td>
</tr>
<tr>
<td>Antiepileptics</td>
<td>7</td>
<td>3.9</td>
</tr>
<tr>
<td>Amino-penicillin</td>
<td>6</td>
<td>3.4</td>
</tr>
<tr>
<td>Analgesics</td>
<td>6</td>
<td>3.4</td>
</tr>
<tr>
<td>Allopurinol</td>
<td>6</td>
<td>3.4</td>
</tr>
<tr>
<td>Antibacterial sulfonamides/nevirapinea</td>
<td>4</td>
<td>2.3</td>
</tr>
<tr>
<td>Traditional drugs</td>
<td>3</td>
<td>1.7</td>
</tr>
<tr>
<td>Antihypertensive drugs</td>
<td>2</td>
<td>1.1</td>
</tr>
<tr>
<td>Quinine</td>
<td>2</td>
<td>1.1</td>
</tr>
<tr>
<td>Abacavir</td>
<td>1</td>
<td>0.6</td>
</tr>
<tr>
<td>Chinese drug of undetermined nature</td>
<td>1</td>
<td>0.6</td>
</tr>
<tr>
<td>Not determined</td>
<td>17</td>
<td>9.6</td>
</tr>
<tr>
<td>Total</td>
<td>177</td>
<td>100</td>
</tr>
</tbody>
</table>

a The antibacterial sulphonamide was cotrimoxazole.
b Mixed decoctions of medicinal plants and ingredients.

SJS / TEN and ARV Pathophysiology

• Adverse drug reactions
  – Type B
    • Unpredictable
    • Not dose-dependent
  – Immune-mediated (allergic)
  – T-cell mediated
  – Direct cell death

SJS / TEN and ARV Pathophysiology

• ARV involved
  – NRTI
    • Abacavir*
    • Didanosine
    • Zidovudine
  – NNRTI
    • Nevirapine
    • Delavirdine
    • Efavirenz
    • Etravirine
    • Rilpivirine
  – PI
    • Fosamprenavir
    • Darunavir
    • Indinavir
    • Lopinavir/Ritonavir
    • Atazanavir
  – INSTI
    • Dolutegravir*
    • Raltegravir
  – EI
    • Maraviroc*

SJS / TEN and ARV
Clinical presentation

• Skin manifestations
  – Prodrome: hyperesthesia / pain “sunburnt-like”
  – Atypical “targetoid” lesions
    • Erythematous, dusky or purpuric
  – Flaccid blisters
  – Painful erosions
  – Mucosal ulceration
    • 2 or more areas affected
    • Haemorrhagic and painful

SJS / TEN and ARV
Clinical presentation

• Constitutional symptoms
  – Fever, malaise, anorexia, pharyngodynia
• Systemic manifestations
  – Pulmonary
  – Haematologic
  – GI/Liver
  – Cardiovascular
  – Neurologic

SJS / TEN and ARV
Clinical presentation

1. Bullous EM: epidermal detachment <10% BSA, localised typical target or raised atypical targets, only one mucosa involved

2. Stevens-Johnson syndrome (SJS): epidermal detachment <10% BSA, widespread erythematous or purpuric macules or flat atypical targets, haemorrhagic erosions of the mucosae (2 or more)

3. SJS and toxic epidermal necrolysis (TEN) overlap: epidermal detachment 10-30% BSA with skin lesions

4. TEN with spots: epidermal detachment >30% BSA with skin lesions

5. TEN without spots: large sheets of epidermal detachment >10% BSA without skin lesions

SJS / TEN and ARV
Differential diagnoses

• Erythema Multiforme
• Staphylococcal scalded skin syndrome
• Acute GVHD (Graft vs Host Disease)
• Linear IgA dermatosis
• DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms)
• “TEN-like” eruptions
  – LE (Lupus Erythematosus)
  – Lymphoproliferative disorders

SJS / TEN and ARV
Work up

• Laboratory
  – Blood, urine and stool
  – Cultures
• ECG
• Imaging
  – Lung
  – Heart
  – CNS

SJS / TEN and ARV Work up

- Skin biopsy

SJS / TEN and ARV Management

• General measures
  – Consult with Burn Unit staff
  – ABC assessment
  – Full examination
  – Nutritional support
  – Pain control
  – Skin and mucous membranes care

Model of Care
NSW Statewide Burn Injury Service

ACI Statewide Burn Injury Service 2012. Available from:
SJS / TEN and ARV Management

- Skin and wound care
  - Cleansing
  - Dressing
    - Consider long-term dressings
    - Consider antimicrobial compounds (eg. Silver) for wound bacterial colonisation control
  - Prophylactic antibiotics not recommended

SJS / TEN and ARV Management

• Pharmacologic therapies
  – Intravenous immunoglobulin
  – Cyclosporine
  – Corticosteroids
  – N-acetyl cysteine
  – Biologics: anti-TNFα

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SJS / TEN and ARV
Management

- Genetic studies
  - HLA B*5701 (Abacavir)
  - CYP2B6 and HCP5 polymorphism (Nevirapine)

- Offending drug
  - Do not reintroduce
  - Desensitisation?

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