Cutaneous Adverse Drug Reactions (CADR) in TB and HIV

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Outline

• Introduction
• Significant types of CADR in TB
• Initial management in acute stage
• Rationale behind rechallenging
• The rechallenge process and its pitfalls
• Special types of TB CADR
• Adverse drug reactions (ADR) contributed to the death of 2.9% of patients in adult medical wards of four geographically diverse hospitals in SA

• Overall mortality rate was 18 per 100 admissions, and 16% of these deaths were ADR related

• Antiretrovirals, antiTB drugs and co-trimoxazole were the most commonly implicated drugs

• Anti-infective-associated ADR is a major cause of mortality in our setting

• The incidence of CADR is significantly higher in HIV-infected persons
• However, not all forms of CADR have an increased incidence in HIV
• Urticaria, angioedema, lichenoid drug eruptions, vasculitis and fixed drug eruptions are not more common in HIV-infected persons
• The most common phenotypes in HIV are Stevens Johnson syndrome and toxic epidermal necrolysis (SJS/TEN) and Drug rash with eosinophilia and systemic symptoms (DRESS syndrome) accounting for >90% of cases

Toxic epidermal necrolysis
Drug Reaction with Eosinophilia and Systemic Symptoms (DHS/DRESS)
Do CADR present differently in HIV?

• No evidence that the reactions are more severe
• No large population studies on mortality and morbidity associated with HIV-associated CADR
• Looking at our data for the last 10 years at Groote Schuur
  – TEN mortality is 9% only on supportive care
  – This compares more than favourably with > 30% in developed countries
• Our population is younger: this may be the explanation for our low mortality

Management of TB-associated CADR

• All anti-TB drugs should be stopped when the initial CADR suspected

• Allow the skin and internal organs to return to a well-documented baseline
Multidisciplinary approach

TB-associated CADRs are multi-organ diseases that often require expertise ranging from hepatologists, infectious disease specialists, pulmonologists, dermatologists, dietitians and others.

The best outcomes are attained using a multidisciplinary approach.
• DOES THE PATIENT HAVE TUBERCULOSIS?
• ARE YOU AS A CLINICIAN CONFIDENT OF THE DIAGNOSIS OF TUBERCULOSIS?
• IS IT WORTH RE-EXPOSING THIS PATIENT TO A POTENTIALLY LIFE-THREATENING DRUG or can they be managed on 2\textsuperscript{nd} line TB drugs?
• ARE THE SEQUELAE OF CADR AMENABLE TO THE DRUGS YOU INTEND TO USE?
Rechallenging first-line drugs in TB-associated CADR

• Rechallenge is a prolonged process
• Median duration of hospitalization is 50 days in our recent study
• \text{1}^{\text{st}} \text{ initiate a bridge therapy of 3 second-line drugs to which the patient was not previously exposed to minimize risk of resistance}


FOR HOW LONG SHOULD I CONTINUE THESE BEFORE INTRODUCING \text{1}^{\text{ST}}\text{ LINE AGENTS?}
Multiple drug hypersensitivity reactions to anti-tuberculosis drugs: five cases in HIV-infected patients

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<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug susceptibility testing</td>
<td>INH-resistant, RMP-susceptible</td>
<td>RMP- and INH-susceptible</td>
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<td>RMP- and INH-susceptible</td>
<td>RMP- and INH-susceptible</td>
</tr>
<tr>
<td>Initial treatment for TB</td>
<td>Rifabutin*</td>
<td>Rifabutin*</td>
<td>Rifabutin*</td>
<td>Rifabutin*</td>
<td>Rifabutin*</td>
</tr>
<tr>
<td>Type of initial CADR</td>
<td>DHS</td>
<td>SIS/TEN</td>
<td>DHS</td>
<td>SIS/TEN</td>
<td>DHS</td>
</tr>
<tr>
<td>Second-line TB drugs used as</td>
<td>OFX, ETH and SM</td>
<td>OFX, ETH and SM</td>
<td>OFX, ETH and SM</td>
<td>OFX, ETH and SM</td>
<td>OFX, ETH and SM</td>
</tr>
<tr>
<td>cover before rechallenge</td>
<td>SM; within 10 min; itch, erythema and facial edema, followed by generalised</td>
<td>ORX, ETH or SM; fever, headache, itch, conjunctivitis, generalised edema,</td>
<td>SM; fever, morbilliform rash, conjunctivitis, chills, headache, oedema and</td>
<td>SM; fever, hepatitis and eosinophilia within 3 days</td>
<td>SM; fever, hepatitis and eosinophilia within 3 days</td>
</tr>
<tr>
<td>Reactions to cover drugs</td>
<td>burning pain worse on the hands and feet, nausea, increased blood pressure, elevated creatine kinase, hepatitis; nerve conduction studies showed peripheral neuropathy of small fibres ORX, 10 min after ingestion; nausea, burning, generalised pain, painful hands and feet; facial oedema, increased blood pressure</td>
<td>burning sensation orally, hepatitis, median sensorimotor neuropathy, peroneal neuropathy, and oedema; these features recurred within 20 min when the 3 drugs were re-introduced; none was re-introduced again</td>
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</tr>
<tr>
<td>Reactions during the rechallenge process to first-line drugs</td>
<td>None</td>
<td>RIF after 4 days: oedema, itch, eosinophilia and facial oedema INH, after 3 days: itch, erythema and eosinophilia</td>
<td>RIF after 4 days: oedema, itch, eosinophilia and facial oedema INH, after 3 days: itch, erythema and eosinophilia</td>
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</tr>
<tr>
<td>Route of administration leading to reaction</td>
<td>Oral, 1; injection, 1</td>
<td>Oral, 3; injection, 1</td>
<td>Oral, 2</td>
<td>Oral, 2</td>
<td>Oral, 2</td>
</tr>
<tr>
<td>Treatment on discharge</td>
<td>EMB, ETH, RMP, PZA</td>
<td>RMP, ETH, EMB, PZA</td>
<td>RMP, INH, EMB, terizidone</td>
<td>AMK, OFX and ETH</td>
<td>RMP, EMB and PZA</td>
</tr>
<tr>
<td>CTCAE grading of most severe reaction</td>
<td>Peripheral neuropathy Grade 3</td>
<td>Peripheral neuropathy Grade 3</td>
<td>Oedema Grade 2</td>
<td>Hepatitis Grade 3</td>
<td>SIS/TEN overlap Grade 4</td>
</tr>
</tbody>
</table>

*Combination tablet of RMP, INH, ETH and EMB.

MDH = multiple drug hypersensitivity; INH = isoniazid; RMP = rifampicin; TB = tuberculosis; CADR = cutaneous adverse drug reaction; DHS = drug hypersensitivity syndrome; SIS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis; OFX = ofloxacin; ETH = ethionamide; SM = streptomycin; AMK = amikacin; CMV = cyto megalovirus; PZA = pyrazinamide; CTCAE = common terminology criteria for adverse events.
52. *what percentage had mdhs

53. tab mdhs

<table>
<thead>
<tr>
<th>mdhs</th>
<th>Freq.</th>
<th>Percent</th>
<th>Cum.</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>63</td>
<td>64.29</td>
<td>64.29</td>
</tr>
<tr>
<td>Yes</td>
<td>35</td>
<td>35.71</td>
<td>100.00</td>
</tr>
<tr>
<td>Total</td>
<td>98</td>
<td>100.00</td>
<td></td>
</tr>
</tbody>
</table>
• The most commonly implicated 2nd line drugs are fluoroquinolones (ofloxacin or moxifloxacin), streptomycin and ethionamide.
• Kanamycin also induced reactions, but <<< frequently
Hypotheses

• Non-specific immune dysfunctional and dysregulated immune responses in HIV

• Rechallenging too soon after CADR during – recommendation ranges from 6 weeks to 6 months
• The excessive immune responses confirmed with patch testing and skin prick testing in the same cohort
• Rechallenges reactions in HIV-infected participants characterized by systemic rather than localized reactions

Fig. 1. (a) Monomorphous folliculocentric papules on a background of erythema extending beyond the area of the patch test, which was performed on the back. (b) Palmar erythema with areas of focal necrosis.

Shebe K, Ngwanya MR, Gantsho N, Lehloenya RJ. Contact Dermatitis. 2014 Feb;70(2):125-7
Message

A third of patients will develop a clinically significant ADR on exposure to a TB drug they have not previously encountered.

The implicated 2\textsuperscript{nd} line drugs are fluoroquinolones (ofloxacin or moxifloxacin), streptomycin and ethionamide.

95\% of these occur within 10 days.
Rechallenge with first-line drugs

IS THE STRAIN(S) OF TB SENSITIVE TO THE DRUGS YOU ARE GOING TO RE-EXPOSE THE PATIENT TO?

CONFIRM DURATION OF Rx (if already on the continuation phase, no need for PZA & EMB)
The drugs should be rechallenged **sequentially** and **additively**
Sequence of rechallenge

• The order the drugs are rechallenged based on the knowledge that, of the 4 first line agents, INH has the highest early bactericidal activity followed respectively RIF, PZA and lastly EMB.

• We hypothesize that this sequence is the most likely to minimize development of drug resistance and offer the best mycobacterial suppression during the potentially prolonged rechallenge process.


Current cohort of 98 patients

Confirmed rechallenge reactions

| Offending drug | RIF (n=21) | INH (n=23) | PZA (n=19) | EMB (n=16) |
Message

• All 4 first line drugs cause significant proportion of both forms SJS/TEN and DRESS
• The assumption absolving EMB is wrong and dangerous
Features of a rechallenge reaction

• Itch, hepatitis and fever were the most frequent reactions in 23 patients occurring in 48, 39 and 35% of the patients respectively


• In our cohort of 98 patients, the commonest features were erythematous followed by hepatitis itch, eosinophilia, fever and oedema in that order
<table>
<thead>
<tr>
<th>Feature</th>
<th>Total number of incidents*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Itch</td>
<td>11 (48)</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>9 (39)</td>
</tr>
<tr>
<td>Fever</td>
<td>8 (35)</td>
</tr>
<tr>
<td>Erythema</td>
<td>4 (17)</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (13)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (13)</td>
</tr>
<tr>
<td>Oedema</td>
<td>3 (13)</td>
</tr>
<tr>
<td>Rigours</td>
<td>2 (9)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2 (9)</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Leucopenia</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Pain</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>1 (4)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>55</strong></td>
</tr>
</tbody>
</table>

*Some patients presented with more than one feature. There were a mean of 2.4 (1–7) incidents per reaction.
15/1
Reinf
Bacrim
Stalled

1/2
Developed
Rash

1/2
Admitted to
George Hospital

2/3
Skin rash
improved

2/3
Lift improved
Temperature
Springs
T/f to X-ray
County T/f Hosp.

7/3/18
Ted Max
KAN

15/3/18
R. Lemon
Admitted
Max
KAN

21/3
Severed
Eye
All Rx
Stopped

25/3
SS
1/fk

29/3
T/f
Group 16

KAN
Wasp 26
Lesson

- IF YOU ARE GOING TO RECHALLENGE KNOW FEATURES OF A RECHALLENGE REACTION
- HAVE ACCESS TO THOSE “FEATURES”
- EARLY WITHDRAWAL OF THE OFFENDING DRUG SAVES LIVES
Intervals between new drugs

• In 22/23 patients, the rechallenge reactions occurred within 72 h of exposure to the offending drug


• Similar finding in our current cohort
Message

• REINTRODUCE A NEW DRUG AT LEAST AT 4 DAY INTERVALS

• ON THE PROVISO THERE IS NO RECHALLENGE REACTION
Lichenoid drug reaction to antituberculosis drugs treated through with topical steroids and phototherapy

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(a) Lichenoid drug reaction showing depigmentation, hyperpigmentation and fissuring. (c) Clinically treated.
Fig. 5. Lichenoid drug eruption with depigmentation in an HIV-infected man on treatment of a second episode of tuberculosis with Rifafour, a combination drug of rifampicin, isoniazid, pyrazinamide, and ethambutol. The rash initially developed during the first course of tuberculosis treatment and resulted in areas of depigmentation and hyperpigmentation. This picture shows recurrence with violaceous patches within the depigmented areas from the first episode.
Angioedema

- Desensitization is possible but this is highly specialized
I am always happy to advise but I need a complete history always preferably copies of prescription charts and notes

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- Most importantly my Patients