Update on TB-IRIS

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Paradoxical TB-IRIS

- Patient diagnosed with TB and started on TB treatment
- Typically improving on TB treatment then start ART
- Recurrence of TB symptoms and new or recurrent clinical manifestations of TB (Usually 1-3 weeks after starting ART)

8-43% of patients on TB treatment when starting ART develop paradoxical TB-IRIS.
OUTLINE

• Neurological TB-IRIS
• Prolonged TB-IRIS
• Important differential diagnoses
• Corticosteroids
• Pathogenesis
• Risk factors and ART timing
# IRIS meta-analysis

Pooled cumulative incidences as % (95% credibility intervals)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence (%)</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMV retinitis</td>
<td>37.7 (26.6 - 49.4)</td>
<td>-</td>
</tr>
<tr>
<td>Cryptococcal meningitis</td>
<td>19.5 (6.7 - 44.8)</td>
<td>20.8 (5.0 - 52.7)</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>15.7 (9.7 - 24.5)</td>
<td>3.2 (0.7 - 9.2)</td>
</tr>
<tr>
<td>PML</td>
<td>16.7 (2.3 - 50.7)</td>
<td>-</td>
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</tbody>
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*Muller, Lancet Infect Dis 2010;10:251*
Neurological TB-IRIS

- 12% with paradoxical TB-IRIS have CNS involvement
- Up to 47% of TBM patients starting ART develop IRIS
- Features
  - Meningitis
  - Tuberculoma/s
  - Radiculomyelopathy
- Occurs in patients with or without CNS TB prior to ART
- Outcomes
  - 12% mortality and 18% loss to follow-up in one series
  - 25% mortality in another series
  - Neurological disability

Pepper et al, Clin Infect Dis 2009
Marais et al, Clin Infect Dis 2012
TBM diagnosis  

TBM-IRIS

Slide courtesy Suzaan Marais
TBM and PTB prior to ART
TB-IRIS with enlarging mass lesion/cerebral oedema
Patient died
CSF Neutrophils and TBM-IRIS

Marais CID 2012
Prolonged TB-IRIS

- Typically suppurative lymphadenitis & abscesses
- Systemically well
- Tuberculomas & cerebral abscesses

**TB-IRIS duration (n = 176)**
- Median: 70 days
- IQR: 41-111 days
- IRIS > 90 days: 36%

Bana, unpublished
Prolonged TB-IRIS: management

- Often repeated aspirations required
- Avoid surgical drainage
- Repeat TB culture (and DST if positive)
- Role of corticosteroids for more than 4 months questionable unless CNS involved
- Experimental therapies
  - Thalidomide and TNFα-blockers
- Consider prolonging TB treatment
  - How adequate is drug penetration?
Key points in TB-IRIS diagnosis

1. Diagnosis of TB confirmed or very likely?
2. Improvement on TB treatment prior to ART?
3. Symptom onset typically 1-3 weeks on ART
4. Deterioration with inflammatory features of TB
5. Consider and exclude differential diagnoses
6. Exclude drug-resistant TB

No confirmatory diagnostic test
100 TB-IRIS suspects screened using case definition

**KEY FINDING**

Undiagnosed rifampicin resistance in **10.1%** of patients (95% CI 3.9-16.4%) presenting with TB-IRIS, after exclusion of known rifampicin resistance and alternative opportunistic diseases.
Lymph node enlargement

Differential diagnoses

- Lymphoma
- Kaposi’s
- Castleman’s disease

Consider malignancy particularly when LN remains firm

- NTM IRIS
- Cryptococcal IRIS
Hepatic TB-IRIS case

- 4 months treatment for drug-sensitive pericardial TB
- Clinically improved, then started ART
- 3 weeks later presented with fever and hepatomegaly
- LFT: Bil 52, CBil 31, Alk Phos 1081, GGT 1468, ALT 82, AST 88
- CD4 rise from 64 to 221
- Biopsy AFB- and TB culture -

Case courtesy of Mark Sonderup
Hepatic TB-IRIS vs DILI

**Hepatic TB-IRIS**
- RUQ pain, nausea and vomiting
- Tender hepatomegaly
- Cholestatic LFT derangement
- +/- mild jaundice
- Usually other TB-IRIS manifestations

**Drug-induced liver injury**
- Similar symptoms
- Typically not hepatomegaly
- Transaminitis +/- jaundice
- Absence of other TB-IRIS features

Patients may present with clinical picture between these two - Biopsy or treat as DILI

Two conditions may co-exist
## Other important differential diagnoses

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Differential diagnoses</th>
</tr>
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<tbody>
<tr>
<td>Pulmonary infiltrate</td>
<td>Bacterial pneumonia</td>
</tr>
<tr>
<td></td>
<td>PCP</td>
</tr>
<tr>
<td></td>
<td>Kaposi’s sarcoma</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>Bacterial empyema</td>
</tr>
<tr>
<td></td>
<td>Kaposi’s sarcoma</td>
</tr>
<tr>
<td>Meningitis</td>
<td>Bacterial</td>
</tr>
<tr>
<td></td>
<td>Cryptococcal</td>
</tr>
<tr>
<td>Space-occupying lesion</td>
<td>Toxoplasmosis</td>
</tr>
<tr>
<td></td>
<td>Cryptococcuma</td>
</tr>
<tr>
<td></td>
<td>Primary CNS lymphoma</td>
</tr>
<tr>
<td>Fever with general deterioration</td>
<td>Bacterial sepsis</td>
</tr>
<tr>
<td></td>
<td>NTM</td>
</tr>
<tr>
<td></td>
<td>Kaposi’s or lymphoma</td>
</tr>
</tbody>
</table>

*Consider and investigate for DR-TB in all scenarios*
Randomised controlled trial of prednisone vs placebo
GF Jooste Hospital, Cape Town, 2005-8

• 110 participants
• Life-threatening TB-IRIS was an exclusion
• Prednisone (or placebo) dose
  – 1.5 mg/kg/d for 2 weeks then
  – 0.75 mg/kg/d for 2 weeks
• Open-label prednisone at physician discretion if clinical deterioration/relapse

Meintjes, AIDS 2010
## Primary endpoint

Cumulative number of days hospitalized and outpatient therapeutic procedures (counted as 1 additional day), ITT analysis

<table>
<thead>
<tr>
<th></th>
<th>Placebo arm N = 55</th>
<th>Prednisone arm N = 55</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td>Total days hospitalized</td>
<td>463</td>
<td>282</td>
<td>-</td>
</tr>
<tr>
<td>Total number outpatient procedures</td>
<td>28</td>
<td>24</td>
<td>-</td>
</tr>
<tr>
<td><strong>Cumulative primary endpoint (median, IQR)</strong></td>
<td><strong>3 (0-9)</strong></td>
<td><strong>0 (0-3)</strong></td>
<td><strong>0.04</strong></td>
</tr>
</tbody>
</table>
Secondary endpoints

- Consistent benefit, maximal in first 4 weeks, across a range of secondary outcome measures
  - Symptom score
  - Karnofsky performance score
  - MOS-HIV questionnaire (quality of life assessment)
  - Chest radiology score
  - C-reactive protein

- 10/55 in prednisone arm relapsed after completing study drug and required re-initiation of prednisone
  - 4 weeks appeared to be too short for these patients
## Adverse events

<table>
<thead>
<tr>
<th></th>
<th>Placebo arm</th>
<th>Prednisone arm</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death on study</td>
<td>2 (4%)</td>
<td>3 (5%)</td>
<td>0.65</td>
</tr>
<tr>
<td>Corticosteroid side effects while on study drug*</td>
<td>3 (5%)</td>
<td>8 (15%)</td>
<td>0.11</td>
</tr>
<tr>
<td>Infections while on study drug</td>
<td>17 (31%)</td>
<td>27 (49%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Severe infections**</td>
<td>4 (7%)</td>
<td>2 (4%)</td>
<td>0.40</td>
</tr>
</tbody>
</table>

* Included BP > 140/90, oedema, hyperglycaemia, hypomania, acne, Cushingoid features, gastritis symptoms

** WHO stage 4 or invasive bacterial infection
Corticosteroids for paradoxical TB-IRIS?

Symptom improvement
Reduced hospitalisation
? Survival benefit in life threatening cases

Potential adverse effects
- Kaposi’s
- Infections
- Metabolic
Diagnostic uncertainty
CASE: 49 year old HIV+ man with CD4=29, diagnosed with drug-susceptible PTB. Started ART 2 weeks after TB treatment. 2 weeks later developed recurrent TB symptoms, worsening of pulmonary infiltrate and new pleural effusion.

MANAGEMENT: Antibiotic, aspiration of pleural effusion, prednisone. TB cultures of sputum and effusion were negative at TB-IRIS.
Pathogenesis of paradoxical IRIS

- Recovery of pathogen-specific immune responses and T-cell activation
- Recovery of innate immune function
- Inflammatory reactions directed to antigens of opportunistic infection
- Pro-inflammatory cytokines and chemokines
- Defective immune regulatory function
Hypercytokinaemia accompanies HIV-tuberculosis immune reconstitution inflammatory syndrome

Tadokera, Eur Resp J 2011;37:1248

22 TB-IRIS vs 22 controls
Controls were HIV-TB patients sampled at 2 weeks on ART

- IL-6
  - IRIS: 250 pg/ml
  - Non-IRIS: 50 pg/ml
  - p-value: 0.0002

- IFN-γ
  - IRIS: 200 pg/ml
  - Non-IRIS: 50 pg/ml
  - p-value: 0.003

- TNF-α
  - IRIS: 400 pg/ml
  - Non-IRIS: 100 pg/ml
  - p-value: 0.0003
Major TB-IRIS risk factors

• Low CD4 count

• Short interval between TB treatment and ART

• Disseminated TB
When to start ART after recent diagnosis of OI?

Several recent clinical trials
SAPiT IRIS incidence
(IRIS cases/100 person years)
ART timing and primary endpoints

- Death
  - p = 0.006
  - 38% ↓

- Death/AIDS
  - p = 0.45

- Death
  - p = 0.45
ART timing and primary endpoints in patients with CD4 < 50

* CAMELIA data represents all patients in trial, majority had CD4 < 50 (median CD4 = 25)
Implications

• In patients with CD4 < 50: start ART at 2 weeks
  – Even though more likely to develop IRIS with early ART
  – Benefit most from early ART in terms of survival and preventing AIDS events

• In patients with CD4 > 50
  – ART can be deferred ~ 8 weeks to reduce risk of IRIS
  – Except patients with severe clinical disease, organ system dysfunction, low performance score, low BMI or Hb as these are associated with higher mortality
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