TB-IRIS

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HIV viral load response to ART

ART commenced

1-2 log drop in VL over first 2 weeks of ART

Kuritzkes, JID 2007
Suppression of HIV replication on ART

Early reversal of immune suppression (systemically and at tissue level)

Inflammatory reactions

Targeted at TB antigens

IRIS = Immune reconstitution inflammatory syndrome

Clinical deterioration with TB-IRIS
Patients on TB treatment

ART

Paradoxical TB-IRIS

Patients not on TB treatment

ART

ART-associated TB

Unmasking TB-IRIS
Paradoxical TB-IRIS characteristics

• Incidence 8 – 54% (15.7% in meta-analysis)
• Onset of symptoms: Median 14 days from ART start
• Hospitalisation in up to 48%
• Median duration
  – 2-3 months in literature
  – 69 days (IQR = 38-106) in our cohort studies (n=217)
• Mortality infrequent
  – Meta-analysis 3.2% (CNS TB-IRIS = 25-75%)

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 1-4 weeks on ART
4. Deterioration with inflammatory features of TB
5. Consider and exclude differential diagnoses
6. Exclude drug-resistant TB

There is no confirmatory diagnostic test
## Important differential diagnoses

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Differential diagnoses</th>
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<tbody>
<tr>
<td>Lymph node enlargement</td>
<td>Kaposi’s sarcoma, Lymphoma</td>
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<tr>
<td>Pulmonary infiltrate</td>
<td>Bacterial pneumonia, PCP, Kaposi’s sarcoma</td>
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<tr>
<td>Pleural effusion</td>
<td>Bacterial empyema, Kaposi’s sarcoma</td>
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<tr>
<td>Meningitis</td>
<td>Bacterial, Cryptococcal</td>
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<tr>
<td>Space-occupying lesion</td>
<td>Toxoplasmosis, Cryptococcoma, Primary CNS lymphoma</td>
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<tr>
<td>Fever with general deterioration</td>
<td>Bacterial sepsis, NTM, Kaposi’s or lymphoma</td>
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</table>
Severity: wide spectrum

Recurrent fevers and night sweats

Fatal enlargement of cerebral tuberculoma complicated by cerebral oedema
Major TB-IRIS syndromes

1. Lymphadenitis
2. Pulmonary
3. Neurological
4. Abdominal
5. Serositis (effusions)
6. Features of systemic inflammation
   - High fevers, marked tachycardia, weight loss

83% multisystem manifestations in our cohort studies
Lymphadenitis

- 40% of TB-IRIS cases
- Prominent features of “acute inflammation”
- Typically suppurate within weeks
- Independent predictor of prolonged IRIS (>90 days)
  - aOR = 2.7 (95% CI = 1.3 - 6.0)
- 6/217 patients in our cohort studies had IRIS > 365 days
  - typically suppurative lymphadenitis

Bana et al, unpublished
Recurrent cough, with worsening pulmonary infiltrate and cavitation
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
  - 13% mortality and 18% loss to follow-up in one series
  - 25% and 75% mortality in other series
  - Neurological disability

Pepper et al, Clin Infect Dis 2009
Marais et al, Clin Infect Dis 2012
Agarwal et al, AIDS Res Ther 2012
CSF Neutrophils and TBM-IRIS

- TBM diagnosis Day 0
- ART Start Day 14
- 2 weeks post ART/IRIS Day 28

Marais CID 2012
TBM and PTB prior to ART
TB-IRIS with enlarging mass lesion/cerebral oedema
Patient died
Abdominal features

- Lymph node enlargement
- Abscess formation
- Peritonitis and ascites
- Liver involvement
- Splenic involvement and rupture
- Intestinal involvement
- Renal involvement
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
Pericardial effusion with tamponade (1 litre drained)

New right pleural effusion
Rationale for steroid trial
- Anecdotal reports of symptomatic response
- Potential risks in patients with advanced HIV

110 participants (55 each arm)

Life-threatening TB-IRIS was an exclusion

Open-label prednisone at physician discretion if clinical deterioration/relapse

Meintjes et al, AIDS 2010;24:2381
HIV-TB patients recently started ART with suspected TB-IRIS

Assessed using a clinical case definition for TB-IRIS and alternative diagnoses excluded

Inclusion criteria
Informed consent
Randomised

Prednisone
1.5mg/kg/day x 2 weeks
0.75mg/kg/day x 2 weeks

Identical placebo
1.5mg/kg/day x 2 weeks
0.75mg/kg/day x 2 weeks

Followed for a total of 12 weeks
Primary endpoint: Total number of days hospitalised + outpatients therapeutic procedures
Secondary endpoints included symptom score, CXR score and steroid side effects
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>
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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>Cumulative primary endpoint (median, IQR)</td>
<td>3 (0-9)</td>
<td>0 (0-3)</td>
<td>0.04</td>
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Significant reduction in morbidity associated with prednisone treatment
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
Prednisone treatment for TB-IRIS

• No excess of severe infections or metabolic side effects with 4 week course of prednisone

• Based on these findings
  – If clinical diagnosis of TB-IRIS is made and other reasons for deterioration excluded
  – And symptoms are significant
  – Prednisone starting at 1.5mg/kg/d is indicated
Steroids for TB-IRIS: other points

• Effective for symptom control
• In most cases unlikely to have survival benefit
  – Apart from neurological TB-IRIS
• Reasonable to defer steroids until sure of diagnosis
  – Exclude or treat for other possibilities
• Average duration of TB-IRIS is 2-3 months, but many cases shorter
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.
Other management

• NSAID in milder cases

• Needle aspiration
  – Suppurative lymphadenitis/abscesses
  – Effusions

• ART interruption
  – CNS involvement with depressed level of consciousness
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