TB-IRIS

Research priorities and update from Kampala workshop

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TB-IRIS

- “Unmasking” of untreated TB
- Paradoxical deterioration on TB treatment
Paradoxical TB-IRIS
TB-IRIS paradoxical reactions

- Incidence: 8-45%
- Median 2-4 weeks after ART initiation
- Risk factors
  - Shorter interval between TB treatment and ART initiation
  - Disseminated TB
  - Low baseline CD4 and high baseline VL
  - Vigorous CD4/VL response to ART
- Life threatening complications described but mortality rare

TB-IRIS in resource constrained settings

- Higher burden of TB in ART programmes
  - 23% of those initiating ART on concurrent TB treatment (Lawn 2006)

- Clinical expertise, investigations and treatment options limited

- Anticipate greater impact on morbidity and mortality

- Prospective cohort studies needed
Challenges in diagnosis
No diagnostic test; diagnosis of exclusion

**ADDITIONAL DIAGNOSIS**
- Bacterial infections
- Fungal infections
- NTM infections
- Malignancies

**DRUG RESISTANCE**
13/141 in Cape Town cohort of TB-IRIS suspects had MDR or Rifampicin monoresistant

**DRUG REACTION**
- Drug fever vs TB-IRIS fever
- Hepatic involvement
Explosion of tuberculin-specific Th1-responses induces immune restoration syndrome in tuberculosis and HIV co-infected patients

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\textit{AIDS} 2006, 20:F1–F7
Case definition (1)

- **Diagnosis of HIV and TB** – WHO criteria
- **Response to TB treatment** – improved/stabilised
- **On ART**
  - Response documented by >1 log decrease in HIV RNA, though seldom available
- **Onset** within 3 months (up to 6) of starting/changing ART
- **Exclusion of alternative explanation**
  - TB treatment failure due to drug resistance
  - Another opportunistic infection or neoplasm
  - Drug toxicity or reaction
  - Complete non-adherence to ART
Case definition -(2)

Clinical criteria

Major

1) New/enlarging lymph nodes, cold abscesses or other focal tissue involvement
2) New/worsening radiological features of TB
3) Breakthrough TB meningitis or new/enlarging focal CNS lesion
4) New or worsening serositis

Minor

1) Constitutional symptoms- e.g., fever, night sweats
2) Respiratory symptoms - e.g., cough, dyspnea, stridor
3) Abdominal pain and/or hepatomegaly
4) Resolution of clinical and/or radiological findings without change in TB treatment

1 major or 2 minor
Treatment: corticosteroids

- Case reports documenting response
- Potential complications
  - KS, herpes reactivations and other side effects
- Many cases self-limiting
- Dose and duration?
Randomised controlled trial
Prednisone vs placebo for mild and moderate TB-IRIS
Cape Town, South Africa

- Severe TB-IRIS excluded
  - Neurological, respiratory failure, airway compromise
- Prednisone or placebo
  - 1.5 mg/kg/d x 2 weeks then 0.75 mg/kg/d x 2 weeks
- Primary endpoints
  - Hospitalisation and procedures
- 62 of 100 patients enrolled

Meintjes, Rebe, Rangaka, Pepper, Wilkinson, Maartens
Prevention

Optimal timing of ART initiation in those on TB treatment?

EARLY

IRIS and other concerns

DELAYED

Risk of disease progression and death
“Unmasking” TB-IRIS
“Unmasking” TB-IRIS in developing country settings

- High rates of incident TB in the period after ART initiation
  - 17.6/100 person years (Bonnet 2006)
  - 23/100 person years in first 90 days (Lawn 2006)
- Cases of accelerated TB (John 2006)
- Background of high TB incidence in those not on ART
- Unclear extent of role IRIS plays in the presentation of incident TB early after ART initiation
Post-ART TB

- Is the **incidence** of TB increased in first 6 months of ART?

- Is the **presentation** of TB accelerated?

- Are **paradoxical reactions** more common?

- What is the most effective method to **screen** for active TB prior to ART initiation?
PRIORITY ISSUES

1. Validation of case definition for paradoxical TB-IRIS

2. Defining the role of steroids in treatment of paradoxical TB-IRIS

3. Timing of ART in patients on TB treatment

4. Screening for active TB pre-ART
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