TB meningitis: the clinical research agenda

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Wellcome Trust Major Overseas Programme
Viet Nam
TB meningitis: pathogenesis

Bacteremia

↑Inflammation

↑bacteria

DEATH (25%)

Arnold Rich
1893-1968

TB meningitis: pathology

- Basal meningitis
- Hydrocephalus
- Infarcts
- Tuberculomas
Why study TB meningitis?

Conservative estimate: 100,000 cases each year

Log rank P<0.001
Why study TB meningitis?

The human model

- In hospital care (1-2 months)
- Serial cerebrospinal fluid (CSF) samples
- Serial brain imaging with CT and MRI
- High ‘event’ frequency
TBM is a medical emergency

Treatment before the onset of coma is the greatest benefit a physician can give a patient with TBM
The problem: rapid diagnosis

Clinical algorithms

CSF ZN stain, microscopy, culture

GeneXpert

Can we get to this?
Key research questions

- Is GeneXpert ULTRA more sensitive than current GeneXpert for TBM diagnosis?
- How will we rapidly detect drug resistant bacteria?
- Will NGS technologies (e.g. MinION) allow rapid bacterial detection and drug resistance?
- Are there novel host/bacterial biomarkers?
TBM treatment

Enhance bacterial killing

Control intra-cerebral inflammation
Intra-cerebral drug penetration

Levofloxacin
Moxifloxacin

INH

PZA

New agents e.g. bedaquiline
delaminid

Rifampin
ETH
SM

Blood-brain barrier
Intensified regimen containing rifampicin and moxifloxacin for tuberculous meningitis: an open-label, randomised controlled phase 2 trial

Rovina Ruslami*, A Rizal Ganiem*, Sofiati Dian, Liqa Apriani, Tri Hanggono Achmad, Andre J van der Ven, George Borm, Rob E Aarnoutse, Reinout van Crevel

60 Indonesian Adults. Oral rifampicin (450mg) vs IV 600mg for 1st 2 weeks

817 Vietnamese adults. Standard regimen vs rifampicin 15mg/kg + levofloxacin (1g/day)
For 1st 2 months
Controlling intracerebral inflammation: adjunctive dexamethasone

545 Vietnamese adults. 6-8 week dexamethasone vs placebo

Adjunctive steroids and HIV-associated TBM?

### 3.1.1 HIV-positive

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Corticosteroid Events</th>
<th>Corticosteroid Total</th>
<th>Control Events</th>
<th>Control Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thwaites 2004</td>
<td>27</td>
<td>44</td>
<td>37</td>
<td>54</td>
<td>32.3%</td>
<td>0.90 [0.67, 1.20]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td>44</td>
<td>54</td>
<td></td>
<td>32.3%</td>
<td>0.90 [0.67, 1.20]</td>
</tr>
</tbody>
</table>

Total events: 27
Heterogeneity: Not applicable
Test for overall effect: Z = 0.73 (P = 0.47)

### 3.1.2 HIV-negative

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Corticosteroid Events</th>
<th>Corticosteroid Total</th>
<th>Control Events</th>
<th>Control Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thwaites 2004</td>
<td>57</td>
<td>227</td>
<td>67</td>
<td>209</td>
<td>67.7%</td>
<td>0.78 [0.58, 1.06]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td>227</td>
<td>209</td>
<td></td>
<td>67.7%</td>
<td>0.78 [0.58, 1.06]</td>
</tr>
</tbody>
</table>

Total events: 57
Heterogeneity: Not applicable
Test for overall effect: Z = 1.60 (P = 0.11)

Total (95% CI): 271/263 = 100.0%
Heterogeneity: Chi² = 0.43, df = 1 (P = 0.51); I² = 0%
Test for overall effect: Z = 1.76 (P = 0.08)
Test for subgroup differences: Chi² = 0.39, df = 1 (P = 0.53), I² = 0%
### Impact on neuro-disability?

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Corticosteroid n/N</th>
<th>Control n/N</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up 2 to 24 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kumarvelu 1994</td>
<td>0/24</td>
<td>1/23</td>
<td></td>
<td>1.6%</td>
<td>0.32 [0.01, 7.48]</td>
</tr>
<tr>
<td>Girgis 1991</td>
<td>14/145</td>
<td>27/135</td>
<td></td>
<td>29.1%</td>
<td>0.48 [0.26, 0.88]</td>
</tr>
<tr>
<td>Lardizabal 1998</td>
<td>10/29</td>
<td>14/29</td>
<td></td>
<td>14.6%</td>
<td>0.71 [0.38, 1.34]</td>
</tr>
<tr>
<td>Schoeman 1997</td>
<td>14/70</td>
<td>19/71</td>
<td></td>
<td>19.7%</td>
<td>0.75 [0.41, 1.37]</td>
</tr>
<tr>
<td>Malhotra 2009</td>
<td>11/65</td>
<td>5/32</td>
<td></td>
<td>7.0%</td>
<td>1.08 [0.41, 2.85]</td>
</tr>
<tr>
<td>Thwaites 2004</td>
<td>34/274</td>
<td>22/271</td>
<td></td>
<td>23.0%</td>
<td>1.53 [0.92, 2.54]</td>
</tr>
<tr>
<td>Prasad 2006</td>
<td>5/41</td>
<td>3/46</td>
<td></td>
<td>2.9%</td>
<td>1.87 [0.48, 7.34]</td>
</tr>
<tr>
<td>Chotmongkol 1996</td>
<td>4/29</td>
<td>2/30</td>
<td></td>
<td>2.0%</td>
<td>2.07 [0.41, 10.44]</td>
</tr>
</tbody>
</table>

**Subtotal (95% CI)**: 677 / 637

**Total events**: 92 (Corticosteroid), 93 (Control)

**Heterogeneity**: Chi² = 11.85, df = 7 (P = 0.11); I² = 41%

**Test for overall effect**: Z = 0.60 (P = 0.55)

<table>
<thead>
<tr>
<th>Follow-up at 5 years</th>
<th>Corticosteroid n/N</th>
<th>Control n/N</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thwaites 2004</td>
<td>17/128</td>
<td>18/116</td>
<td></td>
<td>100.0%</td>
<td>0.86 [0.46, 1.58]</td>
</tr>
</tbody>
</table>

**Subtotal (95% CI)**: 128 / 116

Prasad K, Singh MB, Ryan H.

Corticosteroids for managing tuberculous meningitis.

How does dexamethasone save lives?

Thwaites et al. Lancet Neurol. 2007
Green J et al. PLOS One. 2009
**LTA4H Genotype determines survival and dexamethasone responsiveness**

Survival in 182 HIV uninfected Vietnamese adults with TBM treated with or without Adjunctive dexamethasone

Tobin et al Cell. 2012; 148, 434–446
Will more directed, ‘intelligent’ host-directed therapies improve outcome?

- Aspirin
- Thalidomide
- Anti-TNF biologicals
- Interferon-gamma
- Developing list of ‘rational’ candidates
Critical care and TBM

Sodium/hyponatraemia

Temperature

Glucose/diabetes

Mechanical Ventilation

Nutrition

Rehabilitation
Active trials (search 21/5/17)

- Adjunctive aspirin for HIV-uninfected adults with TBM (Vietnam – complete)

- Optimizing Treatment to Improve TBM Outcomes in Children (TBM-KIDS) (India – recruiting)

- High-dose Rifampicin for the Treatment of Tuberculous Meningitis: a Dose-finding Study (ReDEFINe) (Indonesia – not recruiting)

- Adjunctive Corticosteroids for Tuberculous Meningitis in HIV-infected Adults (The ACT HIV Trial) (Vietnam – opens Wednesday!)

- Leukotriene A4 Hydrolase Stratified Trial of Adjunctive Corticosteroids for HIV-uninfected Adults With Tuberculous Meningitis (Vietnam – opens October 2017)

- The Relationships Between Gene Polymorphisms of LTA4H and Dexamethasone Treatment for Tuberculous Meningitis (China – not recruiting)

**Funding awaited:**

- Short intensive anti-tuberculosis and anti-thrombosis treatment for children with tuberculous meningitis (SURE trial) (Africa, Vietnam)
Current and future clinical research priorities

Prevention
• Vaccine: Adult/HIV-infected

Diagnosis
• High sensitivity; resistance detection

Treatment
• PK optimised regimens; old and new drugs
• Can we improve upon corticosteroids?
• Precision/personalised anti-inflammatory therapy?
• Evidence-based critical care
Thank you