Delamanid Central Nervous System Pharmacokinetics in Tuberculous Meningitis

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Disclosures

• Otsuka provided Delamanid for the animal studies
**Background: CNS Tuberculosis**

- Most severe form of extrapulmonary TB
- **TB meningitis (TBM)** accounts for 0.5-1%
- Disproportionately high mortality and morbidity
  - Young children
  - HIV co-infection
- Meningeal exudate
- Hydrocephalus
- Vasculitis leads to strokes

References:

Background: Treatment

• **Fatal** without treatment

• Current regimen for sensitive
  – RIF, INH, PZA, S (adult)
  – RIF, INH, PZA & EMB (children)
  – Steroids

• **Poor CNS penetration**
  – EMB, RIF

• **Multidrug Resistance (MDR):**
  – Rifampin-resistance associated with **94%** mortality
  – HIV-associated TBM:
    • INH-resistance **1.78 fold** increased risk of death
    • MDR-TBM uniformly **fatal**

Vinnard C CID 2017; Tho DQ AAC 2012; Ruslami R Lancet ID 2013; Heemskerk AD NEJM 2016
Exudative Meningitis and Tuberculoma

Neurobehavioral Deficits

Tucker et al, DMM 2016
$^{11}$C-Rifampin PET Bioimaging

- Rifampin is **KEY** anti-mycobacterial
- Bactericidal BUT poor CNS penetration
- Dynamic PET imaging to elucidate pharmacokinetics and penetration into lung granuloma

DeMarco, Jain et al 2015
Paucity of $^{11}$C-Rifampin Signal in Brain

Tucker, Ordonez, Peloquin, Jain et al, Manuscript Under Review
Paucity of $^{11}$C-Rifampin Signal in Brain

M. tuberculosis-Infected

Tucker, Ordonez, Peloquin, Jain et al, Manuscript Under Review
Decreased $^{11}$C-Rifampin Penetration into Brain Lesion with Treatment

**Time-activity curves (TAC) of ONE rabbit imaged over weeks of treatment**

**Area under the curve (AUC) ratios of brain lesion/plasma comparing ALL rabbits imaged over weeks of treatment**

Tucker, Ordonez, Peloquin, Jain et al, Manuscript Under Review
Rifampin Mass Spec shows Decreased Rifampin Penetration Overtime

Tissue/tissue ratio (brain/plasma)

Week 0 2 3 4 0 2 3 4

Brain (lesion) CSF

Tucker, Ordonez, Peloquin, Jain et al, Manuscript Under Review
Background: Delamanid

- New TB drug by Otsuka Pharmaceutical Co., Ltd.
- Nitro-dihydro-imidazooxazole derivative
- Active against *Mycobacterium tuberculosis*
  - Inhibits mycolic acid synthesis
  - $\text{MIC}_{95}$ on agar media w/ 0.5% albumin = 12 ng/mL
- Side effects: Prolonged QTc, depression, headache
- Currently approved in European Union, Japan & Korea for 2nd line therapy (2014)
  - MDR
    - Improved sputum clearance in pulm MDR-TB
- PK studies in rats demonstrated distribution into CNS, eyes, placenta and fetus
  - Higher levels in tissue compared to plasma

Sasahara K DMM 2015; Shibata M BDD 2017; Gler MT ENJM 2012;
Delamanid Rabbit Protocol

• 6-7 weeks old (~ teenagers)
  – Uninfected (PBS)
  – Infected (M. tuberculosis)

• Delamanid 5 mg/kg via NG

• Plasma
  – 1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 12, 24, 36, & 48 hr

• CSF & Brain sample
  – Terminal samples
  – 9 & 24 hr
**Delamanid Results**

Cmax of adults from trials: median = 357 ng/mL (range 124-1000); \( \text{MIC}_{95} = 12 \text{ ng/mL} \)
**Delamanid Results**

**MIC**

$\text{MIC}_{95} \ 12 \ \text{ng/mL}$

**Graphs**

- **CSF**
  - Delamanid Infected: Blue
  - DM-6705 Infected: Red
  - Delamanid Uninfected: Green
  - DM-6705 Uninfected: Purple

- **Brain**
  - Delamanid Infected: Blue
  - DM-6705 Infected: Red
  - Delamanid Uninfected: Green
  - DM-6705 Uninfected: Purple
Delamanid Results

Delamanid CSF/Plasma ratio

Delamanid Brain/Plasma ratio

- **Infected**
- **Control**
Clinical Relevance

• So what about patients?
Patient with TBM-Mumbai

- 26 year old female
- No co-morbidities or hx of TB/TB contact
- Presentation:
  - Cough, fever, HA with decrease vision bilaterally
  - CSF GeneXpert: *M. tuberculosis* detected
    - Rifampin resistance detected
- Imaging:
  - Brain MRI: meningeal enhancement with tuberculomas
- Course:
  - Started on 2nd line drugs & steroids
  - MGIT confirmed XDR-TBM
  - Initially good clinical & radiologic improvement
  - **BUT relapsed** 3 months after treatment stopped
  - **Delamanid** started & clinical samples obtained 5 wks later
    - Capreomycin, Meropenem, Augmentin, Clofazimine, Linezolid, Cycloserine, *para*-aminosalicylic acid (PAS)
Patient with TBM-Philippines

- 35 year old male
- HIV+
- Presentation:
  - Diagnosed October 2016
  - CSF: WBC 147 cells/µL, protein 96.10 mg/dL
  - CSF: culture grew *M. tuberculosis*; smear AFB+
    - Rifampin & INH resistance detected
- Course:
  - Started on Levofloxacin, Amikacin, Prothionamide, Linezolid, Meropenem, Bactrim, Augmentin
  - Initially improvement (CSF WBC 6 cells/µL, protein 64.57)
  - **BUT worsened** with RLE weakness with new nodules on MRI
    - CSF WBC 486 cells/µL, protein 5319.89
  - **Delamanid** started & clinical samples obtained 5 months later
    - Meropenem, Bedaquiline, Linezolid, Bactrim, Augmentin
## Delamanid Results

<table>
<thead>
<tr>
<th>Sample</th>
<th>Concentration (ng/mL)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Delamanid (Lab 1)</td>
<td>Delamanid (Lab 2)</td>
<td>DM-6705</td>
</tr>
<tr>
<td>Plasma T = 0 HR</td>
<td>550</td>
<td>773.5</td>
<td>109.3</td>
</tr>
<tr>
<td>Plasma T = 2 HR</td>
<td>450</td>
<td>572.6</td>
<td>86.3</td>
</tr>
<tr>
<td>Plasma T = 4 HR</td>
<td>750</td>
<td>1082.8</td>
<td>96.3</td>
</tr>
<tr>
<td>Plasma T = 7 HR</td>
<td>740</td>
<td>848.3</td>
<td>95</td>
</tr>
<tr>
<td>CSF (4h) No Heparin</td>
<td>BLQ</td>
<td>1.9</td>
<td>0.7</td>
</tr>
<tr>
<td>CSF w/ Heparin</td>
<td></td>
<td>1.7</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Mumbai with XDR TBM
Delamanid 100mg BID

**CSF/Plasma ratio = 0.16%**

Philippines with XDR TBM
Delamanid 100mg BID

**CSF/Plasma ratio = 7%**

Cmax of adults from trials: median = 357 ng/mL (range 124-1000); MIC\textsubscript{95} 12 ng/mL
Patients – Where are they now?

• **Mumbai**
  – Completed 24 weeks of Delamanid
  – Off steroids
  – No HA or vision changes

• **Philippines**
  – Currently still receiving Delamanid (along with Bedaquiline and Linezolid)
  – Off steroids
  – Awake and alert
  – Receiving rehab to improve ambulation
Conclusions

• Delamanid CSF levels are low in TBM patients and rabbits
• High Delamanid brain levels in rabbits compared to plasma
  – Trend for higher in uninfected brain

• Can drugs with low CSF concentrations but high brain concentrations work for TBM?
  – CSF has low numbers of bacilli with unknown viability
  – Unknown degree & effect of protein binding
  – Antifungals work:
    • Amphotericin and Isavuconazole for Cryptococcus (low CSF levels)
    • Echinocandins for Candidal meningoencephalitis (poor CSF penetration but good efficacy)

• In order to develop optimal regimens, there need to be more preclinical and clinical data coupled with PK-PD modeling to integrate the data
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