Novel Therapies for NTM

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Disclosures

- **Past**: Cooperative Research & Development Agreement (CRADA) with Insmed, Inc.
- **Current**: CRADA with Matinas Biopharma
- **Off-label use**: aerosolized amikacin sulfate
- **Investigational use**: amikacin liposome inhalation suspension
Learning objectives

- Understand the challenges involved in drug development for NTM
- Consider aspects of clinical trial design such as endpoint selection, efficacy and safety assessments, sample size, and trial length which need to be optimized to facilitate development of novel therapies
Question #1

Which of the following is not a challenge for NTM drug development:

- Requirement for lengthy multi-drug regimen
- Concomitant infections with bacteria such as Pseudomonas aeruginosa
- Overlapping coverage of M. tuberculosis
- Time required to assess efficacy
Which of the following is *not* a challenge for NTM drug development:

- Requirement for lengthy multi-drug regimen
- Concomitant infections with bacteria such as *Pseudomonas aeruginosa*
- Overlapping coverage of *M. tuberculosis*
- Time required to assess efficacy
Drug development for NTM - Challenges

- Introducing novel drug into a multi-drug regimen
- Resistance with monotherapy
- Need for prolonged treatment course
- Length of time required to see effect
- Environmental reservoirs with common acquisition of new infections
- Concomitant airway infections
  - Bug-bug interactions
  - Bug-drug interactions
- For inhaled therapies
  - Distribution to cavities, air trapping, inflamed/obstructed airways
- Intracellular & extracellular killing
- Hostile environment for getting drugs to bugs
  - Biofilm formation
  - Viscous & purulent airway secretions
Amikacin: Pros & Cons

- Active against many mycobacteria
- Readily available therapeutic monitoring
- Resistance
  - Known mechanism for high-level resistance
  - Reasonable clinical correlation with in-vitro susceptibility tests
- Very narrow therapeutic window
  - Ototoxicity common
  - Vestibular toxicity
  - Nephrotoxicity
Inhaled Amikacin for Treatment of Refractory Pulmonary Nontuberculous Mycobacterial Disease

Kenneth N. Olivier¹, Pamela A. Shaw², Tanya S. Glaser¹, Darshana Bhattacharyya¹, Michelle Fleshner¹, Carmen C. Brewer³, Christopher K. Zalewski³, Les R. Folio⁴, Jenifer R. Siegelman⁵, Shamira Shalom⁶, In Kwon Park¹, Elizabeth P. Sampaio¹, Adrian M. Zelazny⁶, Steven M. Holland⁵, and D. Rebecca Prevots¹

- Retrospective study n=20
- Treatment refractory
- Inhaled amikacin added to failing regimen
  - 250 mg/ml diluted 3 mL saline
  - Jet nebulizer
  - Started 250mg once daily
  - Dosing limited by dysphonia
  - Titrated toward 500mg bid
    - 250 mg daily (50%)
    - 250 mg twice daily (20%)
    - 250 mg thrice weekly (15%)

| Sex, female, n (%) | 16 (80) |
| Age, mean (SD), yr | 56 (16) |
| Comorbidities, n (%) |
| CFTR carriers | 3 (15) |
| Cystic fibrosis | 2 (10) |
| Chronic obstructive pulmonary disease | 2 (10) |
| Asthma | 1 (5) |
| Primary ciliary dyskinesia | 1 (5) |
| CT findings |
| Initial score, mean (SD) | 6 (3) |
| Cavitary disease, n (%) | 9 (45) |
| Mycobacterium species, n (%) |
| *Mycobacterium abscessus* group | 15 (75) |
| *Mycobacterium avium* complex | 5 (25) |
| Mo on mycobacterial treatment |
| 60 (6, 190) (before amikacin), median (range) |
Question #2

All the following are adverse effects of amikacin that may be less common with inhalation of the drug:

- a. Ototoxicity
- b. Dysphonia
- c. Vestibular toxicity
- d. Nephrotoxicity
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- **Months on inh amikacin**
  - 19 (1, 50)

- **Toxicity**
  - 7 (35%) stopped

<table>
<thead>
<tr>
<th>Reasons for stopping</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ototoxicity</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Reversible increase in Cr</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Persistent dysphonia</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Vertigo</td>
<td>1 (5)</td>
</tr>
</tbody>
</table>

Liposomal amikacin sustained release formulation developed for inhalational Rx of lung infection

- Key features
  - Charge neutral highly biocompatible liposomes (~0-3 µm)
  - Penetration of drug into biofilm
  - High lung Cmax, AUC, and t½ → improved AUC:MIC ratio
  - Potent PsA killing, including resistant isolates
  - Virulence factors secreted by Pseudomonas facilitate further release of amikacin from liposomes
  - Normal BAL macrophage activity
  - Toxicology in dogs and rats (3-6 months) supports long-term clinical indication
Randomized Trial of Liposomal Amikacin for Inhalation in Nontuberculous Mycobacterial Lung Disease

Kenneth N. Olivier¹, David E. Griffith², Gina Eagle³, John P. McGinnis II³, Liza Micini³, Keith Liu³, Charles L. Daley⁴, Kevin L. Winthrop⁵, Stephen Ruoss⁶, Doreen J. Addrizzo-Harris⁷, Patrick A. Flume⁸, Daniel Dorgan⁹, Matthias Salathe¹⁰, Barbara A. Brown-Elliott², Renu Gupta³,¹¹, and Richard J. Wallace, Jr.²

Randomized 90 Patients (1:1) Stratified:
- CF vs. Non-CF
- MAC vs. Mabs

Primary Endpoint: Efficacy
- Change on semi-quantitative scale for mycobacterial culture at day 84

Secondary endpoints included:
- Proportion of subjects with negative sputum culture for NTM at day 84
- Change in distance walked in the 6-minute walk test at day 84

Culture negative
Growth in liquid medium only
1–49 colonies
1+ (50–100 colonies)
2+ (>100–200 colonies)
3+ (>200–500 colonies)
4+ (>500 colonies)
Primary Endpoint: Change baseline SQS
Secondary endpoint: Negative culture Day 84

Olivier. Am J Respir Crit Care Med 2017
Tertiary endpoint: 6 min walk distance Day 84

Olivier. Am J Respir Crit Care Med 2017
Treatment-emergent AEs

**Double-Blind Phase**

- Dysphonia
- Infective exacerbation of...
- Cough
- Oropharyngeal pain
- Fatigue
- Chest discomfort
- Hemoptysis
- Nausea
- Infective pulmonary...
- Pyrexia
- Wheezing
- Abdominal discomfort
- Dyspnea
- Ear pain
- Headache
- Insomnia
- Laryngitis
- Nasal congestion
- Nasopharyngitis
- Pneumonia
- Diarrhea

- **Percentage of Patients**

**Screened** (n = 136)

- **Randomized** (n = 90)
  - **mITT** (n = 89)

**Completed Study Drug Dosing**

- **LAI + SOC** (n = 44)
- **Placebo + SOC** (n = 45)

- **Open-label LAI** (n = 78)

- **Completed Study Drug Dosing** (n = 59)

- 9 discontinued study drug
  - 1 death (unrelated)
  - 1 SUSAR

- 19 discontinued study drug
  - 1 death (unrelated)
  - 1 SUSAR

- 46 screen failures

- 2 declined open label
12-month post treatment follow-up
At 12 mo f/u, culture converters:

- Less likely **died** during f/u (NS)
  - 1/18 (6%) culture converters
  - 6/47 (13%) non converters
- More likely had **negative culture** at 12-mo f/u (p<0.01)
  - 14/17 (82%) converters
  - 9/31 (29%) non converters
- Less likely on anti-mycobacterials at 12-mo f/u (NS)
  - 4/18 (22%) converters
  - 20/47 (43%) non converters

<table>
<thead>
<tr>
<th>Age</th>
<th>Gender</th>
<th>NTM Infection</th>
<th>CF</th>
<th>Double-Blind Arm</th>
<th>LAI Exposure</th>
<th>Culture Conversion</th>
<th>Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>80</td>
<td>Female</td>
<td>MAC</td>
<td>No</td>
<td>LAI</td>
<td>Discontinued DB (Day 29)</td>
<td>NO</td>
<td>COPD and respiratory failure caused by disease progression</td>
</tr>
<tr>
<td>77</td>
<td>Female</td>
<td>Mabs</td>
<td>No</td>
<td>LAI</td>
<td>Completed OL</td>
<td>NO</td>
<td>Respiratory failure</td>
</tr>
<tr>
<td>62</td>
<td>Female</td>
<td>MAC</td>
<td>No</td>
<td>PBO</td>
<td>Completed OL</td>
<td>NO</td>
<td>Respiratory failure</td>
</tr>
<tr>
<td>57</td>
<td>Female</td>
<td>MAC</td>
<td>No</td>
<td>PBO</td>
<td>Completed OL</td>
<td>NO</td>
<td>Respiratory failure caused by disease progression</td>
</tr>
<tr>
<td>19</td>
<td>Female</td>
<td>Mabs</td>
<td>Yes</td>
<td>PBO</td>
<td>Discontinued OL (Day 143)</td>
<td>NO</td>
<td>Exacerbation of CF, disease progression, retroperitoneal bleed, and kidney failure</td>
</tr>
<tr>
<td>54</td>
<td>Female</td>
<td>MAC</td>
<td>No</td>
<td>PBO</td>
<td>Completed OL</td>
<td>NO</td>
<td>Progression of MAC infection</td>
</tr>
<tr>
<td>57</td>
<td>Male</td>
<td>MAC</td>
<td>No</td>
<td>PBO</td>
<td>Completed OL</td>
<td>YES</td>
<td>Respiratory failure and pulmonary fibrosis</td>
</tr>
</tbody>
</table>
Liposomal amikacin deposition/retention

- Amikacin loaded liposomes labeled with 7mCi 99mTc
- Delivered via customized eFlow nebulizer
- Inertial impaction tests yielded 65% of nebulized 99mTc-LAI in 2.1-3.3 µm range
- Subjects (n=4) inhaled 99mTc-LAI via tidal breathing, seated in front of gamma camera
- Imaged over 120 minutes and 24hr post inhalation
Liposomal amikacin deposition/retention

42% Remaining in nebulizer, tubing, filter

15% Deposited in oropharynx, esophagus, stomach

43% Deposited in lungs

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 min</td>
</tr>
<tr>
<td>Patients with NTM infection</td>
<td>100% (C/P = 2.05)</td>
</tr>
<tr>
<td>(n = 4)</td>
<td></td>
</tr>
<tr>
<td>Healthy males</td>
<td>100% (C/P = 1.63)</td>
</tr>
<tr>
<td>(n = 3)a</td>
<td></td>
</tr>
</tbody>
</table>
Liposomal amikacin deposition/retention

Coronal chest CT

Cobalt-57 transmission

0 minutes

120 minutes

24 hours
Top-line results released Sept 5, 2017

n=336 adult, non-CF patients

Randomized 2:1 to amikacin liposome inhalation suspension (ALIS) + guidelines based therapy (GBT) vs GBT alone

Culture conversion at 6 months

- ALIS + GBT: 29%
- GBT alone: 9% (p<0.0001)

No difference between 2 groups in 6MWT distance

- Culture converters had greater improvement in 6MWT than non-converters (p=0.01)

Time to conversion approximately 30% longer for GBT alone when compared to patients on ALIS plus GBT (p < 0.0001).
Inhaled NO for *M. abscessus*

- Compassionate use intermittent 30 min treatments NO 160 ppm 3-5 times/day over 3 weeks added to failing antibiotic regimen
  - Patient 1 – 19yo progressive *M. abscessus* for 7 years, failed multiple treatment regimens, FEV1 100→50%
  - Patient 2 – 13yo progressive *M. abscessus* for 2 years, failed treatment, FEV1 110-65%, subacute deterioration

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Yaacoby-Bianu. Pediatr Infect Dis J 2017
Question #3

- **Potential advantages of inhaled therapy for NTM:**
  
a. Delivery of higher doses of drug to site of infection
b. Less systemic side effects
c. No need for intravenous access
d. All of the above
Answer #3

- Potential advantages of inhaled therapy for NTM:
  - a. Delivery of higher doses of drug to site of infection
  - b. Less systemic side effects
  - c. No need for intravenous access
  - d. All of the above
Potential for delivery of high doses to site of active infection
Can have microbiologic effect when added to failing systemic antibiotics
Airway toxicity is a concern
Need novel early-phase trial designs & more efficient routes to registration trials for rare disease
  Need validated functional & QOL indicators
    - 6MWT?
    - QOL-B-NTM module?
  Need validated, early microbiologic effect indicators
  Need to be specific to target population
    - Semi-quantitative culture analysis appeared reliable in treatment-naïve MAC lung disease Griffith. Am J Respir Crit Care Med. 2015