Novel Therapies for NTM Disease
NTM Lecture Series for Providers
September, 2018

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Conflict of Interest/Disclaimer

- I was a co-investigator on INS-112, a study of amikacin liposome inhalation suspension for treatment of refractory *M. avium* complex and *M. abscessus* lung diseases
- I am a co-investigator on INS-212 CONVERT and INS-312 CONVERT studies of amikacin liposome inhalation suspension for treatment of *M. avium* complex lung disease
- I am a co-investigator on an Insmed sponsored IIR study of amikacin liposome inhalation suspension for treatment of *M. abscessus* lung disease
- I am a consultant for Insmed
NTM Therapy

• No highly active drugs for most NTM
• NTM lung disease therapy marginally effective
  – 10 (TB)... 5-7(NTM*).......2(IPF)
• No drugs FDA approved for treating NTM lung disease
• Little interest from pharmaceutical industry
• Maybe a little light at the end of the tunnel

*Depends on NTM pathogen
NTM Drug Resistance

- Mutational Resistance
  - *M. tuberculosis*: multiple gene mutations
  - *M. avium* complex:
    - a) 23S rRNA gene (macrolides);
    - b) 16S rRNA gene (amikacin)
  - *M. kansasii*: rpo β gene (rifamycins)
  - *M. abscessus subspecies abscessus/massliense*: 23S rRNA gene (macrolides)

- Inadequate therapy will result in acquired mutational resistance for all of these organisms with potentially profound negative consequences. *Creating* macrolide resistance in MAC and *M. abscessus* subsp is a BIG DEAL.
NTM Drug Resistance

• Innate or “natural” or “cryptic” drug resistance
  – Not readily or predictably associated with in vitro measures of resistance such as MICs
  – Inducible macrolide resistance (erm) gene
  – In vitro susceptibility results may not reliably predict in vivo treatment response:
    – *M. abscessus*
    – *MAC*
    – *M. simiae*
    – *M. justaboutNTMium* complex
Amikacin Liposome Inhalation Suspension (ALIS)
# Inhaled Amikacin

<table>
<thead>
<tr>
<th>Drug</th>
<th>N</th>
<th>Dose, Frequency, Duration</th>
<th>Culture Conversion</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrospective Design – inhaled parenteral amikacin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Davis, 2007</td>
<td>6 MAC</td>
<td>15 mg/kg once daily for &gt; 3mos</td>
<td>67%</td>
<td>33%</td>
</tr>
<tr>
<td>Olivier, 2014</td>
<td>20 MAC</td>
<td>50% received 250 mg/day</td>
<td>25%</td>
<td>35%</td>
</tr>
<tr>
<td>Yagi, 2017</td>
<td>21 MAC</td>
<td>15 mg/kg once daily for &gt; 3mos</td>
<td>38%</td>
<td>8%</td>
</tr>
<tr>
<td>Jhun, 2018</td>
<td>20 MAC</td>
<td>250 mg daily to 500 mg tiw</td>
<td>15%</td>
<td>38%</td>
</tr>
</tbody>
</table>
Amikacin Liposome Inhalation Suspension (ALIS)

• ALIS\(^{a}\) is amikacin sulfate (590 mg amikacin base)\(^{b}\) encapsulated in liposomes for inhalational delivery

• ALIS was designed to increase amikacin uptake into alveolar macrophages, and limit systemic exposure\(^{1-4}\)

\(^{a}\) Previously referred to as Liposomal Amikacin for Inhalation or LAI.

\(^{b}\) 623mg amikacin base per vial; to deliver 590 mg amikacin base to the nebulizer

New drugs: Amikacin Liposome Inhalation Suspension (ALIS) INS-112

- Amikacin Liposome Inhalation Suspension (ALIS)
- ALIS 590 mg vs placebo for 84 days, then open label
- Primary endpoint: reduction in NTM growth by Semi-quantitative sputum cultures: not achieved
- Sputum conversion: 32% in treated group
- 6 min walk distance improved
- Side effects: hoarseness, bronchospasm
- 82.4% who achieved culture conversion after 3 to 6 months of ALIS had negative sputum culture results at 12 months after discontinuation of ALIS.

Olivier KN et al. Am J Respir Crit Care Med 2016;Oct 17
CONVERT Study
Randomized, controlled Phase 3 Study

Population: Adults with treatment-refractory MAC lung disease

Screening and 2:1 randomization

Primary endpoint: Percentage of patients with culture conversion by 6 months

Confirmatory endpoint: Durability of culture conversion

ALIS, amikacin liposome inhalation suspension; GBT, guideline-based therapy; MAC, Mycobacterium avium complex.

a At least 6 months treatment with persistently positive sputum cultures for MAC.

b Final analysis at completion of study is durability of culture conversion 3 months off all MAC treatment for patients who complete 12 months of treatment from the first negative culture that defined conversion.
### CONVERT Study

#### Patient Demographic and Disease Characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ALIS + GBT N = 224</th>
<th>GBT Alone N = 112</th>
<th>Overall N = 336</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean yr (SD)</td>
<td>64.6 (9.6)</td>
<td>64.9 (10.2)</td>
<td>64.7 (9.8)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>165 (73.7)</td>
<td>68 (60.7)</td>
<td>233 (69.3)</td>
</tr>
<tr>
<td>Body mass index, mean kg/m² (SD)</td>
<td>21.4 (3.9)</td>
<td>21.0 (3.8)</td>
<td>NA</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>158 (70.5)</td>
<td>77 (68.8)</td>
<td>235 (69.9)</td>
</tr>
<tr>
<td>Japanese</td>
<td>35 (15.6)</td>
<td>15 (13.4)</td>
<td>50 (14.9)</td>
</tr>
<tr>
<td>Other Asian</td>
<td>23 (10.3)</td>
<td>10 (8.9)</td>
<td>33 (9.8)</td>
</tr>
<tr>
<td>Other/not reported</td>
<td>5 (2.2)</td>
<td>7 (6.3)</td>
<td>12 (3.6)</td>
</tr>
<tr>
<td>Black/African American</td>
<td>3 (1.3)</td>
<td>3 (2.7)</td>
<td>6 (1.8)</td>
</tr>
<tr>
<td>Underlying lung disease, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchiectasis only</td>
<td>146 (65.2)</td>
<td>64 (57.1)</td>
<td>210 (62.5)</td>
</tr>
<tr>
<td>COPD only</td>
<td>29 (12.9)</td>
<td>19 (17.0)</td>
<td>48 (14.3)</td>
</tr>
<tr>
<td>COPD and bronchiectasis</td>
<td>22 (9.8)</td>
<td>18 (16.1)</td>
<td>40 (11.9)</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>26 (11.6)</td>
<td>10 (8.9)</td>
<td>36 (10.7)</td>
</tr>
</tbody>
</table>
**CONVERT Study**

**Primary Endpoint: Culture Conversion by Month 6**

<table>
<thead>
<tr>
<th>ITT Population</th>
<th>ALIS + GBT (N = 224)</th>
<th>GBT Alone (N = 112)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Converter</td>
<td>65 (29.0%)</td>
<td>10 (8.9%)</td>
</tr>
<tr>
<td>Non-Converter</td>
<td>159 (71.0%)</td>
<td>102 (91.1%)</td>
</tr>
</tbody>
</table>

**Adjusted Odds Ratio (95% CI)**

4.220 (2.078, 8.570)

**P Value**

< 0.0001

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*a Culture conversion defined as 3 consecutive monthly MAC-negative sputum cultures by Month 6

*b Adjusted Odds ratio and p-value are calculated using Cochran-Mantel-Haenszel test, with stratification factors of the combination of smoking status and prior GBT as fixed factors.
**CONVERT Study**

Cumulative Rate of Sputum Culture Conversion

Shown at the first month of conversion*

- **ALIS + GBT (N = 224)**
- **GBT Alone (N = 112)**

<table>
<thead>
<tr>
<th>Month</th>
<th>ALIS + GBT</th>
<th>GBT Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>4.9</td>
<td>11</td>
</tr>
<tr>
<td>Month 1</td>
<td>5.4</td>
<td>16</td>
</tr>
<tr>
<td>Month 2</td>
<td>8.0</td>
<td>34</td>
</tr>
<tr>
<td>Month 3</td>
<td>8.9</td>
<td>53</td>
</tr>
<tr>
<td>Month 4</td>
<td>23.7</td>
<td>10</td>
</tr>
</tbody>
</table>

**Adjusted OR (95% CI)** = 4.22 (2.08, 8.57)

*The first of 3 consecutive negative sputum cultures must be achieved by Month 4 to meet the primary culture conversion endpoint by Month 6.*
**CONVERT Study**

**Most Common TEAEs – Safety Population**

<table>
<thead>
<tr>
<th>Preferred</th>
<th>ALIS + GBT N = 223</th>
<th>GBT Alone N = 112</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysphonia</td>
<td>102 (45.7)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Cough</td>
<td>83 (37.2)</td>
<td>17 (15.2)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>48 (21.5)</td>
<td>10 (8.9)</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>39 (17.5)</td>
<td>15 (13.4)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>36 (16.1)</td>
<td>8 (7.1)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>28 (12.6)</td>
<td>5 (4.5)</td>
</tr>
<tr>
<td>Nausea</td>
<td>25 (11.2)</td>
<td>4 (3.6)</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>24 (10.8)</td>
<td>2 (1.8)</td>
</tr>
</tbody>
</table>

TEAEs occurring in >10% of patients in either arm

**TEAE, treatment-emergent adverse event.**
CONVERT Study

Common Adverse Event Onset Over Time

ALIS + GBT (N=223)

GBT Alone (N=112)

Percentage of Patients

Study Month

Dysphonia
Dyspnea
Cough
Oropharyngeal pain
Fatigue
Diarrhea
Nausea
Hemoptysis

^a TEAEs occurring in >10% of patients in either arm.
Summary

• ALIS combined with GBT, improved sputum conversion rates in adults with amikacin-susceptible, treatment-refractory MAC lung disease compared with GBT alone.

• Addition of ALIS to GBT was associated with higher rates of TEAEs, predominantly mild or moderate in severity and respiratory in nature. Incidences of most frequent TEAEs declined after the first month.

• ALIS may have a role in the treatment of refractory MAC lung disease and possibly other MAC therapy roles, such as initial therapy, maintenance therapy, and treatment of other NTM pulmonary pathogens.
Bedaquiline
Bedaquiline and Nontuberculous Mycobacterial Disease

• 2013 Bedaquiline FDA approved for treatment of drug resistant TB
  – Dispensed from ONE pharmacy in the U.S.
  – CDC oversight of all prescription requests

• $30,000/patient for 6 months for Bedaquiline ONLY

• Low MICs and mouse model efficacy against
  – *M. avium* complex
  – *M. abscessus*
**In Vitro Susceptibility Testing of Bedaquiline against *Mycobacterium avium* Complex**

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>MIC range (μg/ml)</th>
<th>MIC&lt;sub&gt;50&lt;/sub&gt; (μg/ml)</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt; (μg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bedaquiline</td>
<td>≤0.008–0.03</td>
<td>≤0.008</td>
<td>0.015</td>
</tr>
<tr>
<td>Amikacin</td>
<td>4–&gt;2048</td>
<td>32</td>
<td>64</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>0.5–&gt;128</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>≤0.5–64</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Linezolid</td>
<td>4–&gt;128</td>
<td>32</td>
<td>64</td>
</tr>
</tbody>
</table>

MIC ranges and concentrations that inhibit the MIC<sub>50</sub> and MIC<sub>90</sub> of 103 strains of *Mycobacterium avium* complex for bedaquiline, amikacin, moxifloxacin, linezolid, and clarithromycin
Preliminary Results of Bedaquiline as Salvage Therapy for Patients with NTM Lung Disease

- Case series of off-label use of bedaquiline for NTM lung disease, 6 MAC, 4 MAB
- Failed at least 12 mo Rx (MAC), 6 mo Rx (MAB)
- Bedaquiline added to best possible companion drugs (mean 5)
- All patients completed 6 months of therapy
- 6/10 microbiologic response, 5/10 at least one negative culture
- Mean Qtc interval change 2.4 msec
- Nausea 60%

Philley, et al Chest 2015
Bedaquiline for Macrolide Resistant MAC Lung Disease

• 9 patients with macrolide resistant MAC lung disease were treated with a multi-drug regimen which included bedaquiline for an average of 20 months.
• The majority of patients had cavitary disease
• An average of 3 companion drugs were used with bedaquiline and all patients had failed prior drug therapy on at least one occasion.
• A decrease in quantitative sputum culture was noted in 7/9 patients at 6 months (78%). 3/9 (33%) of patients converted and remained culture negative for 1 year. Improvement in symptoms was recorded in all patients.
## Clinical Characteristics of Macrolide Resistant MAC Lung Patients Treated with Bedaquiline

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/Sex</th>
<th>Disease Type&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Companion Drugs while on BDQ&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Resistance</th>
<th>Amikacin</th>
<th>Pretreatment</th>
<th>Lowest on BDQ</th>
<th>Bedaquiline MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>58/F</td>
<td>FN + C</td>
<td>EMB, RFB, STR</td>
<td>Yes</td>
<td>Yes</td>
<td>4+</td>
<td>4+</td>
<td>0.015</td>
</tr>
<tr>
<td>2</td>
<td>54/M</td>
<td>NB</td>
<td>EMB, RFB, STR</td>
<td>Yes</td>
<td>Yes</td>
<td>4+</td>
<td>Negative</td>
<td>&lt;0.008</td>
</tr>
<tr>
<td>3</td>
<td>60/F</td>
<td>FN + C</td>
<td>AMK, EMB, RFB, STR</td>
<td>Yes</td>
<td>Yes</td>
<td>3+</td>
<td>1+</td>
<td>0.030</td>
</tr>
<tr>
<td>4</td>
<td>65/M</td>
<td>NB + C</td>
<td>AMK, AZM, EMB, STR</td>
<td>Yes</td>
<td>Yes</td>
<td>3+</td>
<td>Negative</td>
<td>0.015</td>
</tr>
<tr>
<td>5</td>
<td>67/M</td>
<td>NB</td>
<td>EMB, RFB,</td>
<td>Yes</td>
<td>Yes</td>
<td>4+</td>
<td>Negative</td>
<td>0.015</td>
</tr>
<tr>
<td>6</td>
<td>77/F</td>
<td>NB + C</td>
<td>AMK, RFB</td>
<td>Yes</td>
<td>Yes</td>
<td>3+</td>
<td>Negative</td>
<td>Not done</td>
</tr>
<tr>
<td>7</td>
<td>65/F</td>
<td>FN + C</td>
<td>EMB, RFB,</td>
<td>Yes</td>
<td>Yes</td>
<td>3+</td>
<td>8 colonies</td>
<td>&lt;0.008</td>
</tr>
<tr>
<td>8</td>
<td>49/F</td>
<td>C</td>
<td>STR, ETH, RFB, AZI, AMK</td>
<td>Yes</td>
<td>No</td>
<td>3+</td>
<td>No sputum</td>
<td>0.004</td>
</tr>
<tr>
<td>9</td>
<td>72/F</td>
<td>NB/C</td>
<td>ETH, AMK</td>
<td>Yes</td>
<td>Yes</td>
<td>3+</td>
<td>19 colonies</td>
<td>Not done</td>
</tr>
</tbody>
</table>

<sup>a</sup>FN, fibronodular; NB, nodular bronchiectasis; C, cavitary.
<sup>b</sup>AMK, amikacin; AZM, azithromycin; CLR, clarithromycin; EMB, ethambutol; RFB, rifabutin; STR, streptomycin.
# Bedaquiline for Macrolide Resistant MAC Lung Disease

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Baseline/At the start of therapy</th>
<th>1 Month</th>
<th>3 Months</th>
<th>6 Months</th>
<th>12 months</th>
<th>18 months</th>
<th>Total months on Drug</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$4^+$</td>
<td>$3^+$</td>
<td>$4^+$</td>
<td>$4^+$</td>
<td>$4^+$</td>
<td>$4^+$</td>
<td>56 months</td>
<td>Positive</td>
</tr>
<tr>
<td>2</td>
<td>$4^+$</td>
<td>$4^+$</td>
<td>Negative</td>
<td>$3^+$</td>
<td>Off therapy</td>
<td>Off therapy</td>
<td>21 months</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>$4^+$</td>
<td>$1^+$</td>
<td>$3^+$</td>
<td>$4^+$</td>
<td>$4^+$</td>
<td>Off therapy</td>
<td>13 months</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>$4^+$</td>
<td>$2^+$</td>
<td>1 colony</td>
<td>$4$ colonies</td>
<td>Negative</td>
<td>Negative</td>
<td>27 months</td>
<td>Negative</td>
</tr>
<tr>
<td>5</td>
<td>$4^+$</td>
<td>$+$ broth</td>
<td>$1^+$</td>
<td>$+$ broth</td>
<td>Negative</td>
<td>Negative</td>
<td>20 months</td>
<td>Negative</td>
</tr>
<tr>
<td>6</td>
<td>$2^+$</td>
<td>$18$ colonies</td>
<td>Negative</td>
<td>Negative</td>
<td>Off med/culture negative</td>
<td>Off med/culture negative</td>
<td>5 months</td>
<td>Negative</td>
</tr>
<tr>
<td>7</td>
<td>$2^+$</td>
<td>$4^+$</td>
<td>No culture</td>
<td>$8$ colonies</td>
<td>No culture</td>
<td>No culture</td>
<td>6 months</td>
<td>Positive</td>
</tr>
<tr>
<td>8</td>
<td>$3^+$</td>
<td>$3^+$</td>
<td>$3^+$</td>
<td>No sputum</td>
<td>No sputum</td>
<td>Off med/no sputum</td>
<td>10 months</td>
<td>Positive</td>
</tr>
<tr>
<td>9</td>
<td>$4^+$</td>
<td>$2^+$</td>
<td>$23$ colonies</td>
<td>$19$ colonies</td>
<td>$1^+$</td>
<td>41 colonies</td>
<td>23 months</td>
<td>Positive</td>
</tr>
</tbody>
</table>

negative = no bacterial growth; 1+ solid media growth = 50 – 99 colonies; 2+ solid media growth = 100 – 199 colonies; 3+ solid media growth = 200 – 299 colonies; 4+ solid media growth = 300+ colonies; *Unable to produce sputum
**In Vitro** Susceptibility Testing of Bedaquiline Against MAC (Elliott, et al, 2017)

- Metabolized by P-450 (CYP) 3A4 enzyme greatly enhanced in presence of rifampin such that steady state is decreased by 75-80%

Rifabutin has less induction that rifampin (20-fold vs 80-fold)
Bedaquiline and rifamycins

Pharmacodynamics interactions of healthy volunteers with bedaquiline were examined with rifabutin and rifampin using *ex vivo* whole blood cultures

At low concentrations, rifabutin plus bedaquiline yielded greater mycobacterial activity than expected based on individual effects

Representative microbiological response of a patient to BDQ treatment.

Summary

• Bedaquiline may be beneficial in refractory and/or antibiotic resistant NTM lung disease

• Companion drugs are necessary to prevent resistance.

• Further evaluation of mechanisms of resistance and pharmacokinetics warranted
Oxazolidinones

• inhibit protein synthesis by binding at the P site at the ribosomal 50S subunit.

• Linezolid and Tedizolid
Linezolid

- Linezolid XDR-TB
  - 41 patients
  - Failed all available Rx
  - 87% culture conversion at 6 mos
  - Significant dose limiting toxicity
Linezolid for use in NTM

• Retrospective cohort from 6 NTM Rx 102 NTM patients
• 78% pulmonary disease - *M. abscessus* 44%; MAC 33%
  – Median Rx time 21 weeks
  – 600mg daily (79%), 300mg daily (12%)
  – Among PNTM, most stable or improved on Rx
  – Attributable AE’s: 45% at median 20 wks
Tedizolid

- New oxazolidinone formulated to have lower mitochondrial toxicity
- approved for acute bacterial and skin structure infections
- ESTABLISH-1 trial demonstrated noninferiority of 200 mg of oral tedizolid for 6 days vs 600 mg of linezolid twice daily for 10 days in the treatment of adults with ABSSSIs (cellulitis/erysipelas, major cutaneous abscesses, or wound infections).

* Prokopczuk, et al JAMA. 2013
Tedizolid

FIG 1 Concentration-time profiles (mean ± SD) for tedizolid in free plasma (circles), ELF (squares), and AM (triangles) from 20 healthy adult participants.
# Tedizolid

## TABLE 1. Comparison of MICs of linezolid, DA-7157, and DA-7867 for *M. avium* complex and RGM

<table>
<thead>
<tr>
<th>Species (no. of isolates tested) and test agent</th>
<th>MIC (μg/ml)</th>
<th>For 50% of isolates</th>
<th>For 90% of isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>M. avium</strong> complex (13)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linezolid</td>
<td>2–32</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td>DA-7157</td>
<td>1–8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>DA-7867</td>
<td>0.5–8</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td><strong>M. abscessus</strong> (14)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linezolid</td>
<td>8–64</td>
<td>64</td>
<td>64</td>
</tr>
<tr>
<td>DA-7157</td>
<td>0.5–4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>DA-7867</td>
<td>0.5–8</td>
<td>4</td>
<td>8</td>
</tr>
</tbody>
</table>
Tedizolid and Linezolid dosing

Tedizolid - 200-mg tablet taken orally once daily

Linezolid – 300-600 mg daily, 300-600 mg taken orally twice daily

*IV formulations are available
Clofazimine

- “Field SK. Treatment of Mycobacterium avium-intracellulare complex lung disease with a macrolide, ethambutol, and clofazimine”. Chest. 2003
- “Long-term Follow-up of Mycobacterium avium Complex Lung Disease in Patients Treated With Regimens Including Clofazimine and/or Rifampin”. Chest. 2016
- “Clofazimine-containing regimen for the treatment of M. abscessus lung disease” AAC 2017
  - Retrospective review of 42 patients with M. abscessus lung disease treated with clofazimine-containing regimens: 36% initial, 64% added
  - Symptom improvement 81%, radiographic improvement 31%, sputum conversion: 24%
- “Safety and effectiveness of clofazimine for primary and refractory NTM infection” Chest 2017
  - 112 subjects, 24% CF, 78% refractory disease
  - 48% M abscessus “complex”, 37% MAC
  - 41/82 (50%) with pulmonary disease converted to sputum negative
Who knows?

- NO
- GMCSF
How do we test new drugs for treating NTM infections?

- Monotherapy
  - We don’t know the risk for acquired mutational resistance
  - Drugs are too wimpy to do studies similar to those done in TB
- Add on to failing regimen ("monotherapy" trial)
- Part of initial multidrug regimen/comparative trial
- What are the most important endpoints?
  - Sputum conversion
  - Shorter duration of therapy
  - Symptomatic improvement
Future Research Questions Regarding Treatment of MAC?

- 2 vs 3 drugs?
- Role of inhaled amikacin?
- Intensive phase/continuation phase?
- Shorter duration in certain phenotypes?
- Role of new drugs in regimens?
- Role of immune adjuvants?
- How do we prevent reinfection?
NTM Drug Pipeline

State of the Art: Nontuberculous Mycobacteria and Associated Diseases
(Wolinsky, ARRD 1979;119: 107)

• “Proper management requires greater expertise than is needed for treatment of TB, first, to decide who needs to be treated, and second, to determine which drug regimens to use.”

• Sputum conversion rates for MAC lung disease comparable to MDR-TB

• Sputum conversion rates for macrolide resistant MAC lung disease comparable to XDR-TB