Bronchiectasis
2018
A Year in Review

Lucy Morgan
BMed PhD FRACP
Blood Neutrophils Are Reprogrammed in Bronchiectasis

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Amikacin Liposome Inhalation Suspension for Treatment-Refractory Lung Disease Caused by Mycobacterium avium Complex (CONVERT)

A Prospective, Open-Label, Randomized Study

Why did I chose this?
Novel insight into pathogenesis.

Acute neutrophilic inflammation is supposed to
Eliminate invading organisms
Be self limiting
Completely resolve
What's going on here?
Aim:
To assess blood neutrophil phenotype in bronchiectasis when stable and during exacerbation
Methods

Study 1
Stable state
- 8 healthy volunteers
- 8 mild bronchiectasis
- 8 severe bronchiectasis

Day 1: Blood obtained
Day 2: Bronchoscopy

Study 2
Exacerbations
- 6 severe bronchiectasis patients

Day 1 of exacerbation: Blood and sputum obtained
Day 14 of exacerbation: Blood and sputum obtained

Study 3
Community-acquired pneumonia
- 6 patients with no background lung disease

Day 1: Blood obtained
Day 5: Blood obtained
Blood neutrophils survive longer and have less apoptosis in bronchiectasis.
Blood neutrophils in stable bronchiectasis are more activated in an unstimulated state.
Blood neutrophils in bronchiectasis show impaired bacterial phagocytosis and killing.
Neutrophils in the bronchiectatic airway have impaired antibacterial function
conclusion

- stable bronchiectasis
  - the blood neutrophils are reprogrammed to survive longer
- This impairs the neutrophil ability to kill bacteria once recruited to the airway
- This perpetuates the circle
Amikacin Liposome Inhalation Suspension for Treatment-Refractory Lung Disease Caused by *Mycobacterium avium* Complex (CONVERT) A Prospective, Open-Label, Randomized Study

David E. Griffith¹, Gina Eagle², Rachel Thomson³, Timothy R. Aksamit⁴, Naoki Hasegawa⁵, Kozo Morimoto⁶, Doreen J. Addrizzo-Harris⁷, Anne E. O'Donnell⁸, Theodore K. Marras⁹, Patrick A. Flume¹⁰, Michael R. Loebinger¹¹, Lucy Morgan¹², Luigi R. Codecasa¹³, Adam T. Hill¹⁴, Stephen J. Ruoss¹⁵, Jae-Joon Yim¹⁶, Felix C. Ringshausen¹⁷, Stephen K. Field¹⁸, Julie V. Philley¹, Richard J. Wallace, Jr.¹, Jakko van Ingen¹⁹, Chris Coulter²⁰, James Nezamis², and Kevin L. Winthrop²¹; for the CONVERT Study Group*
Why did I chose this?

- NTM infection is an important pathogen in Bronchiectasis
- NTM is notoriously difficult to treat
- CONVERT was a novel study that repurposed an old drug
- Conflict to declare- I was an investigator
AIM:
To evaluate the safety and efficacy of daily Amikacin Liposome Inhalation Suspension (ALIS) Added to standard guideline based therapy (GBT) in patients with refractory MAC lung disease
Methods

Adults with Amikacin sensitive MAC lung disease
MAC (+) sputum culture
Despite 6 months stable GBT
Randomly assigned (2:1) to GBT
**CONVERT**

**INS-212**

**KEY INCLUSION CRITERIA**
- Adult Patients with NTM (MAC) Lung Disease
- Failing at least 6 months of a multi-drug regimen

**INS-312**
- INS-212 non-converters

**INS-212**
- ALIS once daily + Guideline Based Therapy
- Guideline Based Therapy
- Baseline through Month 6

**PRIMARY ENDPOINT**
- Culture Conversion at 6 months

**INS-312**
- ALIS once daily + Guideline Based Therapy
- Guideline Based Therapy
- Up to Month 16

**FULL APPROVAL ENDPOINT 3 Months Off All Treatment**
- 12 months off all treatment
Enrolled 492

Screen failure 156

Randomized 336

ALIS + GBT 224

Withdrawn from study, 44 (19.6%)
  - Patient withdrew, 19 (8.5%)
  - Adverse event, 8 (3.6%)
  - Death, 7 (3.1%)
  - Physician decision, 3 (1.3%)
  - Rescue medication, 1 (0.4%)
  - Other, 6 (2.7%)

Completed study\(^a\) 70 (31.3%)

Continuing study\(^a\) 110 (49.1%)

GBT alone 112

Withdrawn from study, 10 (8.9%)
  - Patient withdrew, 4 (3.6%)
  - Adverse event, 1 (0.9%)
  - Death, 4 (3.6%)
  - Physician decision, 1 (0.9%)

Completed study\(^a\) 76 (67.9%)

Continuing study\(^a\) 26 (23.2%)

62.5% bronchiectasis
14.3% COPD
11.9% BX +COPD

Mean age 64.7 years
69.% F
Top-line Data Indicates CONVERT Study Met Primary Endpoint

- Addition of ALIS to GBT* eliminated evidence in sputum of NTM lung disease caused by MAC by Month 6 in 29% of patients, compared to 9% of patients on GBT alone (p <0.0001)

- **20% absolute difference in treatment groups in favor of ALIS arm**

*Guideline Based Therapy
Top-line CONVERT Study Results – Secondary Endpoints at Month 6

**6-MINUTE WALK DISTANCE (6MWD)**

- No statistically significant difference between patients in the two arms
- Analysis per a pre-specified endpoint shows that patients who achieved culture conversion across both arms demonstrated an improvement in 6-minute walk distance vs. patients who did not culture convert (p=0.0108)

**TIME TO CONVERSION**

- Patients in the GBT-only arm took approximately 30% longer to convert when compared to patients on ALIS plus GBT (p<0.0001)
CONVERT Safety Summary

- Adverse events, consistent with those seen with use of inhaled antibiotics, more frequent in ALIS + GBT arm
- Serious treatment emergent adverse events were similar between treatment arms
- No distinctions between treatment arms of hearing loss or renal impairment

<table>
<thead>
<tr>
<th>SERIOUS TEAES &gt;3%</th>
<th>2:1 Randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients Reporting at Least One Serious Treatment Emergent Adverse Event</td>
<td>20.2% (45)</td>
</tr>
<tr>
<td>System Organ Class</td>
<td>ALIS (n=223)</td>
</tr>
<tr>
<td>Respiratory, Thoracic, Mediastinal Disorders</td>
<td>11.7% (26)</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>2.7% (6)</td>
</tr>
<tr>
<td>COPD (exacerbation)</td>
<td>3.1% (7)</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td>9.0% (20)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>3.6% (8)</td>
</tr>
<tr>
<td>Cardiac Disorders</td>
<td>0.4% (1)</td>
</tr>
<tr>
<td>Patient Deaths</td>
<td>2.7% (6)</td>
</tr>
<tr>
<td>Drop Outs (%)</td>
<td>19.6% (44)</td>
</tr>
<tr>
<td>Total Drop Outs (%)</td>
<td>16.1% (54)</td>
</tr>
</tbody>
</table>
## CONVERT Study Demographics Summary

<table>
<thead>
<tr>
<th></th>
<th>ALIS (n=224)</th>
<th>GBT (n=112)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SMOKERS</strong></td>
<td>11.6% (26)</td>
<td>8.9% (10)</td>
</tr>
<tr>
<td><strong>GUIDELINE BASED THERAPY PRIOR TO ENROLLMENT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ON TREATMENT</strong></td>
<td>89.7% (201)</td>
<td>90.2% (101)</td>
</tr>
<tr>
<td><strong>OFF TREATMENT FOR &gt; 3 MONTHS</strong></td>
<td>10.3% (23)</td>
<td>9.8% (11)</td>
</tr>
<tr>
<td><strong>GEOGRAPHY</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>US</strong></td>
<td>41.5% (93)</td>
<td>42.9% (48)</td>
</tr>
<tr>
<td><strong>ASIA</strong></td>
<td>21.4% (48)</td>
<td>17.9% (20)</td>
</tr>
<tr>
<td><strong>EU + ROW</strong></td>
<td>37.1% (83)</td>
<td>39.3% (44)</td>
</tr>
<tr>
<td><strong>MALE</strong></td>
<td>26.3% (59)</td>
<td>39.3% (44)</td>
</tr>
<tr>
<td><strong>FEMALE</strong></td>
<td>73.7% (165)</td>
<td>60.7% (68)</td>
</tr>
<tr>
<td><strong>MEAN AGE (YEARS)</strong></td>
<td>64.6</td>
<td>64.9</td>
</tr>
</tbody>
</table>
conclusion

• The addition of ALIS to GBT
• For treatment refractory MAC
• Achieved superior culture conversion at 6 M
• Achieved faster culture conversion
• Similar safety profile

An important addition to our toolbox for NTM pulmonary disease
RESPIRE 1: a phase III placebo-controlled randomised trial of ciprofloxacin dry powder for inhalation in non-cystic fibrosis bronchiectasis

Anthony De Soyza, Timothy Aksamit, Tiemo-Joerg Bandel, Margarita Criollo, J. Stuart Elborn, Elisabeth Operschall, Eva Polverino, Katrin Roth, Kevin L. Winthrop and Robert Wilson

RESPIRE 2: a phase III placebo-controlled randomised trial of ciprofloxacin dry powder for inhalation in non-cystic fibrosis bronchiectasis

Timothy Aksamit, Anthony De Soyza, Tiemo-Joerg Bandel, Margarita Criollo, J. Stuart Elborn, Elisabeth Operschall, Eva Polverino, Katrin Roth, Kevin L. Winthrop and Robert Wilson

RESPIRE 1 and 2

Why did I chose these studies?

Focus on phenotype of high risk
Frequent exacerbators
largest trial ever in bronchiectasis
huge effort in R&D
ultimately not positive enough
Important lessons for us all
RESPIRE 1 and 2 study design.

14 days on/14 days off therapy: 12 active cycles over 48 weeks

28 days on/28 days off therapy: 6 active cycles over 48 weeks

Randomisation

8 weeks follow-up after last dose

End of treatment

End of study

Anthony De Soyza et al. Eur Respir J 2018;51:1702052
Patient disposition. RESPIRE 1

N=416
Europe, North America
South America
Australia
Japan

Randomised\# n=416

Ciprofloxacin DPI 14 days on/off n=137
Treated\† n=136 (99.3%)
EOS data available n=111 (81.0%)

Placebo 14 days on/off n=68
Treated n=68 (100%)
EOS data available n=49 (72.1%)

Ciprofloxacin DPI 28 days on/off n=141
Treated n=141 (100%)
EOS data available n=118 (83.7%)

Placebo 28 days on/off n=70
Treated n=69 (98.6%)
EOS data available n=56 (80.0%)

Patients enrolled n=902
Screening failures n=486

Anthony De Soyza et al. Eur Respir J 2018;51:1702052

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Time to first exacerbation for patients receiving ciprofloxacin dry powder for inhalation (DPI) a) 14 days on/off or placebo and b) 28 days on/off or placebo.

Anthony De Soyza et al. Eur Respir J 2018;51:1702052
Descriptive frequency of exacerbations over 48 weeks for patients receiving ciprofloxacin dry powder for inhalation (DPI) a) 14 days on/off or matching placebo and b) 28 days on/off or matching placebo.
RESPIRE 2

N = 521
Asia
Eastern Europe

Patients enrolled
n = 1123

Screening failures
n = 602

Randomised*

n = 521

Ciprofloxacin DPI
14 days on/off
n = 176

Placebo
14 days on/off
n = 88

Ciprofloxacin DPI
28 days on/off
n = 171

Placebo
28 days on/off
n = 86

Treated†

n = 174 (98.9%)

Treated
n = 88 (100%)

Treated
n = 171 (100%)

Treated
n = 86 (100%)

EOS data available*

n = 442

n = 151 (85.8%)

n = 73 (83.0%)

n = 148 (86.5%)

n = 70 (81.4%)

Timothy Aksamit et al. Eur Respir J 2018;51:1702053
No improvement in time to first exacerbation

Time to first exacerbation for patients receiving ciprofloxacin dry powder for inhalation (DPI) a) 14 days on/off or placebo and b) 28 days on/off or placebo.

Timothy Aksamit et al. Eur Respir J 2018;51:1702053
Descriptive frequency of exacerbations over 48 weeks for patients receiving ciprofloxacin dry powder for inhalation (DPI) a) 14 days on/off or matching placebo and b) 28 days on/off or matching placebo.

.RESPIRE 2

No reduction in frequency of exacerbation

Timothy Aksamit et al. Eur Respir J 2018;51:1702053
RESPIRE 1 and 2

- DPI well tolerated in both Cipro and placebo arm
- Resistance
  - Increased MIC to CIPROXIN in both trials
Did the drug work? - Yes

Fixed effects meta-analysis pooling of the four RESPIRE study arms for the European Medicines Agency primary outcome of frequency of exacerbations versus matching placebo.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>log(rate ratio)</th>
<th>se</th>
<th>Weight %</th>
<th>Rate ratio IV, fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>RESPIRE 1 14 day on/off</td>
<td>-0.5</td>
<td>0.208</td>
<td>26.3</td>
<td>0.61 [0.40–0.91]</td>
</tr>
<tr>
<td>RESPIRE 1 28 day on/off</td>
<td>-0.024</td>
<td>0.213</td>
<td>25.1</td>
<td>0.98 [0.64–1.48]</td>
</tr>
<tr>
<td>RESPIRE 2 14 day on/off</td>
<td>-0.19</td>
<td>0.175</td>
<td>37.2</td>
<td>0.83 [0.59–1.17]</td>
</tr>
<tr>
<td>RESPIRE 2 28 day on/off</td>
<td>-0.6</td>
<td>0.315</td>
<td>11.5</td>
<td>0.55 [0.30–1.02]</td>
</tr>
<tr>
<td>Total [95% CI]</td>
<td>100</td>
<td>0.76 [0.62–0.93]</td>
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</tr>
</tbody>
</table>

Heterogeneity: Chi²=3.86, df=3 [p=0.28]; I²=22%
Test for overall effect: Z=2.60 [p=0.009]

Probably best in frequent exacerbators

European Respiratory Society Eur Respir J 2018;51:1752444
What went wrong?

- Heterogeneity
- Geographical and cultural diversity
- 2:1 randomisation means small placebo arm

- RESPIRE 2
  - lots of COPD/Bx overlap
  - Low exacerbation rates 0.6 events/yr/patient
  - (despite inclusion criteria of >2 events/yr)
Blood Neutrophils in stable bronchiectasis?

• A) are the same as sputum neutrophils
• B) are less effective at killing bacteria than those of healthy patients
• C) become more effective during exacerbation
Blood Neutrophils in stable bronchiectasis?

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Amikacin Liposomes Inhalation Suspension (ALIS) in the treatment of NTM pulmonary disease

• A) is effective without guideline based therapy (GBT)?
• B) causes more SAEs than GBT?
• C) in addition to GBT is associated with improved outcomes?
• D) should be recommended as first line for NTM pulmonary disease?
Amikacin Liposomes Inhalation Suspension (ALIS) in the treatment of NTM pulmonary disease

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