Inhaled antibiotics to treat NTM* lung infections

*Nontuberculous Mycobacteria Lung Infection

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Topics

• Why inhaled abx?
  - History in TB/NTM
  - Obstacles
  - Challenges and Prejudice
  - Emerging Evidence
  - Improving Technology
  - Gathering Support

• How inhaled abx?
  - Formulations and Proof of Concept
  - Aerosol Formulation and Device Identification/CMC
  - Microbiology and Animal Studies
  - Clinical Development
Let’s go back to 1950


**AEROSOL STREPTOMYCIN TREATMENT OF ADVANCED PULMONARY TUBERCULOSIS IN CHILDREN**

*Dosage.*—The dosage of streptomycin employed in this study was 2 Gm. daily, administered in two doses of 1 Gm. each, for three to six months. Since

The patients treated were 12 children with various forms of pulmonary tuberculosis, at least 5 of whom had a poor prognosis. The disease in all except the 3 children with atelectatic lesions responded to therapy by apparent healing, the most rapid response occurring in the children with the greatest amount of infiltration, consolidation and cavitation. No significant toxicity or sensitivity reactions occurred in any of the patients or personnel.
History – rational?

Henry Ford’s Wife Wouldn’t Drive Ford Model T, Kept Her Electric Car

April 11th, 2014 by Zachary Shahan

To many, electric cars are a completely new thing. However, they actually have a long history in the United States. For some time, they were the top dog. However, due to battery limitations many decades ago, they got replaced with gasmobiles.

With recent advancements, electric cars are back. But it’s important to note that many of their key benefits are the same today as they were back in the early 20th century.

For example, they are much simpler, cleaner, safer, and nicer to drive. Henry Ford’s wife knew this, as did many women of the early 20th century. Clara Ford apparently wouldn’t drive the Model T. She stuck to her electric car instead, a 1914 Detroit Electric. Here’s more from "TIME" magazine, via the GM-Volt forum:

"Girls dig electric cars. At least that was the marketing message back in 1915, when petrol-powered autos were beginning to decisively pull away from electric ones."
What is the problem with NTM?

Two major bacteria prevalent in non-CF and CF patients:
- *Mycobacterium avium* complex (MAC)
- *Mycobacterium abscessus* complex (MABSC)

- Increasing prevalence, in both CF and non CF
- Serious clinical problem

- Combination oral therapies are given for years
  - Serious side effects from prolonged systemic exposure
NTM Prevalence in the US

- 86,000 estimated cases of NTM lung infections in the US.
- Number is higher than estimates from only a few years ago.
- If the annual 8% increase and the fact that more than 70% of NTM cases are underreported are accounted, the projected number of NTM cases could be as high as 181,000.

https://www.ntmfacts.com/Prevalence:
Estimates are based on national and state-specific NTM case numbers and associated cost, taken from annual inpatient and outpatient visit costs, prescription medications, and previous national NTM studies using Medicare and national survey data.
NTM Prevalence in the US
(a woman’s health issue)

NTM Pulmonary Infections

Symptoms and Pathology

- Chronic cough
- Breathlessness
- Hemoptysis
- Reduced lung function
- Potential respiratory failure
- Bronchiectasis
- Tree-in-bud nodules
- Fibrocavitary disease
- Parenchymal destruction

References:
The Clinical Problem in NTM

• **NTM is driving pulmonary deterioration, and rapid decline in pulmonary function:** Patients with Nontuberculous Mycobacteria (NTM) infection demonstrate 2-5% FEV1 decline/yr.¹

• **Treatment are chronic (given for years):** Current therapeutic options involve many months of oral combination therapy, followed by 1 year post resolution of clinical symptoms²

• **Oral antibiotics have cumulative side effects:** All have chronic accumulative side effects (neurotoxic, nephrotoxic, skin accumulation, etc.)³

• **No inhaled antibiotic are approved yet:** Need tolerable inhaled option to augment oral therapy⁴

References:
2. Floto et al. (2016) Thorax 71: i1-i22
3. Johnson et al. (2014) JTD 6: 210-220
NTM (MABSC and MAC) are destroying lung function, and increasing in prevalence

- NTM infection in CF approx. 13%, and increasing in prevalence within CF\(^1,2\) and within non CF lung disease\(^3,4\)
- MABSC in particular is an aggressive pathogen and leads to rapid loss (>2x) of lung function\(^5\)

Incidence rates of NTM infections in CF, from 2003 (1.4%) to 2011 (8.7%) at the Graub CF Center in Israel\(^6\). Incidence rates in US CF Patients 2017 = ~13%.

Effect on lung function of chronic infection from onset to end stage lung disease in Danish CF patients

References:
Significant Unmet Need in NTM

NTM is emerging threat to patients with lung disease\(^1\): NTM of all pulmonary pathogens is most directly linked to clinical deterioration and death

**Systemic / Oral therapies insufficient\(^2\):** Existing oral drugs, frequently triple therapies and “borrowed” from TB treatments, often insufficient and have tolerability issues, systemic side effects

> 70% of patients undiagnosed\(^3\): Significant patient population with ~86,000 cases diagnosed and ~180,000 total cases in US – rapidly growing medical awareness of many non-diagnosed patients

**Still room for improvement:** *M. abscessus* (key NTM pathogen in CF) remains unaddressed

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**References:**
2. Floto et al. NTM CF Guidelines, 2016
Current NTM therapies are insufficient

- **NTM treatment requires long term oral combination therapy**: Similar to TB, the current therapeutic options are oral antibiotics with high chronic toxicity\(^1\).

- **Treatment outcomes are unsatisfactory**: Discontinuation is frequent (10-30%), and overall treatment success low (40-60\%)\(^2,3\).

- **Inhaled liposomal Amikacin in development**: Phase 3 results indicate culture conversion of NTM, in non CF subjects with MAC infection\(^4\).

What’s the obstacles to consider inhaled therapy in NTM/TB?

Assumptions in the field:

✓ Inhalation is complicated, time consuming and expensive
✓ Mycobacteria need “systemic” treatment, in combination
✓ Inhalation therapy cannot deliver sufficient lung doses of antibiotics

For TB:
- “Inhaled therapy cannot be made sufficiently cheap”

• True?
• Worth reconsidering?
Inhalation PK/PD

Drug exposure following oral (left) and pulmonary (right) delivery illustrating anticipated tissue concentrations

Drugs re-formulated for inhalation have an outstanding track record

<table>
<thead>
<tr>
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<th>TOBI®</th>
<th>CAYSTON®</th>
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<tbody>
<tr>
<td>Active Agent</td>
<td>Tobramycin</td>
<td>Aztreonam</td>
</tr>
<tr>
<td>Nebulizer</td>
<td>LC PLUS® (PARI)</td>
<td>eFlow (PARI)</td>
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<td>Indication</td>
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<td>Novartis Pharmaceuticals</td>
<td>Gilead</td>
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<tr>
<td>Target</td>
<td>Pseudomonas aeruginosa</td>
<td>P. aeruginosa</td>
</tr>
<tr>
<td>Indication</td>
<td>Chronic management, on/off</td>
<td>Chronic management</td>
</tr>
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The history of inhaled therapy in NTM/TB

1950: Inhaled TB therapy with high dose streptomycin\(^1\)
- Very long inhalation times (about 40min.), but indication of clinical benefit (20k higher lung concentration after inhalation than after intramuscular administration)

2016: QIDP designation for MP-376 (inhaled levofloxacin)\(^2\)
- NTM, *P. aeruginosa* pulmonary infections in CF patients.

2017: Insmed’s ALIS reports results from Phase 3 study\(^3\).
- Successful in achieving sputum culture conversion for MAC (32% vs. 9% placebo)

Formulation and Device technologies have improved, and have become less costly

References:
2. https://cysticfibrosisnewstoday.com/2016/03/21/9269/
Emerging Evidence: Inhalable Antibiotics for Pulmonary NTM Infections

- Raptor Pharmaceuticals (now Horizon Pharma) received QIDP designation for MP-376 (inhaled levofloxacin) to treat pulmonary NTM and *P. aeruginosa* infections\(^1\). Quinsair™ is now approved in Canada\(^2\) and Europe\(^3\) to treat *P. aeruginosa* infections. No regulatory approvals for NTM infections to date.

- Insmed’s ALIS (amikacin liposome inhalation suspension) reported positive top-line results from an ongoing phase III study\(^4\) to treat NTM infections\(^5\). Primary endpoint: culture conversion, no change in lung function (%FEV\(_1\)).

- Aradigm’s Lipoquin® and Linhaliq®, both liposomal ciprofloxacin formulations for inhalation, are in pre-clinical development to treat pulmonary NTM infections\(^6\).

References:

Where would we go next?

1. Find efficacy vs. *M. abscessus* (unmet need in CF)
2. Amikacin is potent in MAC, less so in MABSC infections
3. Screen APIs for MICs and formulation challenges:

<table>
<thead>
<tr>
<th>API</th>
<th>MIC vs. MAC (MAC)</th>
<th>MIC vs. MAC (MABSC)</th>
</tr>
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<tbody>
<tr>
<td>Amikacin</td>
<td>4 µg/ml^1</td>
<td>32 µg/ml^2</td>
</tr>
<tr>
<td>QRM-003</td>
<td>0.06 – 0.25 µg/mL^3</td>
<td>0.25 – 1 µg/mL^4</td>
</tr>
<tr>
<td>QRM-006</td>
<td>4 µg/mL^5</td>
<td>1 µg/mL^5</td>
</tr>
</tbody>
</table>

References:
5. Qrumpharma., unpublished results (2017)
Efficacy Studies in Murine Models
QRM-003/QRM-006 (RMI-CSU, ongoing)

Treatment groups:
- a) Control
- b) QRM-003 (Inh.)
- c) QRM-006 (Inh.)
- d) API only (Oral)
- e) API only (I.V.)

Infection with MAC/MABSC

7 days infection

28 days infection (MAC)
7 days infection (MABSC)

Acute Model – 10 Days Treatment

Bacterial Recovery:
- 3 wks. – MAC
- 7 day – MABSC

Euthanasia

Chronic Model –
- 30 Days Treatment (MAC)
- 28 Days Treatment (MABSC)

Drug Distribution:
TBD

Euthanasia
Screening potent NTM Antibiotics for Inhalation

• Criteria:
  • MICs: potent on MABSC and MAC, *but note that MICs may not correlate with clinical response*
  • Dose and Formulation challenges: many NTM antibiotics are very lipophilic, and require re-formulation
  • Airway tolerability and lung penetration: formulation needs to not irritate lung tissue, and remain in lung (or macrophages), rather than being systemically available

• Readout: In vitro/in vivo efficacy model, NTM mice (Colorado State)

• Strategy: Reformulate several antibiotics (overcome solubility/formulation challenges), and select the lead compound for preclinical development upon microbiology/animal testing.
Inhaled Formulations, Antibiotics for Inhalation

- **Nebulizer formulation**
  - Flexible and rapid into human development
  - Deep and accurate lung deposition possible
  - Utilize improved device technology

- **Criteria:**
  - Overcome formulation challenges
  - Osmolarity, pH, salt content
  - Viscosity and output
  - Topical tolerability
  - Predict dose (MIC and animal data both are poor predictors)

- **Steps:**
  - Pilot formulation
  - Aerosol testing, characterization
  - Testing in airway epithelia, animal efficacy models
Inhalation Devices

• Clinical Dose Strategy: We will determine necessary lung dose, then decide on the final nebulization device, depending on efficiency (lung dose) required. Some possible examples depicted.

High peripheral lung deposition; Rapid and convenient delivery

References:
Sample Timeline for NTM Asset

Scope:
- Phase 1 (SAD/MAD, Tolerability)
- Phase 2 “PoC” (short term tx, n=100-120, dose find, micro endpoint)
- Phase 2/3 (24+ weeks, clinical efficacy endpoint, n=250-350)

Assumptions:
- Regulatory strategy will include Orphan and QIDP designation
- Successful PoC study (Ph2B) will move into Phase 3 (with adaptive design)
- Phase 2/3 conducted as two parallel studies (with a total of ~350 subjects)
What to do different (from NTM) in TB

• Inhaled formulation for TB will need to be robust, and feasible for developing world (heat, stability, dose, etc.)

• May be able to use same API as with NTM (potent MIC value for Mtb (0.12-0.25µg/ml))

• Inhalation device: Preclinical development dictated by the need for a low cost, self contained delivery platform for use in low resource settings.

• Inhalation benefits similar to NTM infections (i.e. high lung dose, reduced side effects and reduced amount in systemic circulation).
  • Clinical goal: Reduce disease burden and duration, reduce aerosol transmission
Conclusions

• History and CF development shows inhalation approach is useful for pulmonary mycobacteria infection

• NTM developments pave the way for TB inhaled developments
• Nebulizer therapy has its place, at least in NTM infections

• Next step: demonstrate the utility (*in clinic*) of inhaled antibiotic therapy for mycobacteria infections (NTM)