Non-Cystic Fibrosis Bronchiectasis: Historical Perspective of Product Development

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FDA Public Workshop
Development of Inhaled Antibacterial Treatments for Cystic Fibrosis and Non-Cystic Fibrosis Bronchiectasis
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Introduction

• There are no approved therapies for prevention or management of NCFB exacerbations
• Studies of inhaled antibacterial drugs (tobramycin, gentamicin, aztreonam, colistin, and ciprofloxacin) for the prevention of NCFB exacerbations have yielded mixed results
• Uncertainties regarding duration of treatment, frequency of administration, and appropriate endpoints for this use
• No relevant animal models of NCFB to explore dosing regimen, duration of therapy, and to provide supportive information
Inhaled Antibacterials in NCFB

- **Tobramycin**
  - Barker et al.\(^1\): 4 weeks tobramycin vs. placebo, 2 weeks off drug (N=74); sputum *P. aeruginosa* decreased at week 4; 62% vs. 38% with “improved” medical condition at week 6; no differences in FEV\(_1\) percent predicted at week 4; more adverse events with tobramycin
  - Drobnic et al.\(^2\): 2 6-month cycles tobramycin vs. placebo, 1 month washout, crossover (N=30); fewer admissions, days of hospitalization during tobramycin period; no differences in number of exacerbations, antibiotic use, pulmonary function, quality of life; bronchospasm with tobramycin

- **Gentamicin**
  - Murray et al.\(^3\): 1 year continuous gentamicin vs. placebo (N=65); reduced sputum bacterial density, less sputum purulence, greater exercise capacity, fewer exacerbations, increased time to first exacerbation, improved SGRQ; no differences in pulmonary function; at 3 months post-treatment, outcome measures similar to baseline; bronchospasm with gentamicin

Inhaled Antibacterials in NCFB

• Aztreonam
  – Barker et al.\textsuperscript{1}: 2 trials of 4 weeks aztreonam vs. placebo, 4 weeks off (N=266, 274); no clinically significant differences in adjusted mean change from baseline in QOL-B-RSS at 4 weeks; adverse events more common with aztreonam

• Colistin
  – Haworth et al.\textsuperscript{2}: colistin vs. placebo for up to 6 months (N=144); no significant difference in time to exacerbation; \textit{P. aeruginosa} density reduced at 4 and 12 weeks, SGRQ improved at 26 weeks

\textsuperscript{1}Lancet Respir Med 2014;2:738; \textsuperscript{2}Am J Resp Crit Care Med 2014;189:975
2012 Workshop: Issues in the Design of Clinical Trials for NCFB

• Patient populations
• Treatment of exacerbations vs. prevention
• Clinical trial endpoint measures
  – Disease-specific patient-reported outcome measure: QOL-B
  – Pulmonary exacerbations: time to exacerbation, frequency of exacerbations, other analyses
• Safety: disease vs. tolerability of inhaled therapy
Antimicrobial Drug Advisory Committee Meetings

• NDA 209367: Ciprofloxacin Dry Powder for Inhalation 11/16/17
• NDA 210693: Ciprofloxacin Dispersion for Inhalation 1/11/18
• Programs: 48-week phase 3 trials of intermittent cycles of inhaled ciprofloxacin and placebo; primary endpoint time to first exacerbation, secondary endpoints included frequency of exacerbations, PRO, FEV$_1$ percent predicted
  – Ciprofloxacin DPI: Primary endpoint not met for 3 of 4 test arms, lack of replication of findings across trials, lack of consistency of findings across endpoints in same trial
  – Ciprofloxacin DI: One failed trial, lack of clear explanation for discordant findings between trials
AMDAC Issues for Discussion

• Clinical relevance of the observed treatment effects when risks such as adverse reactions and development of resistance are considered

• Durability of efficacy and safety findings over time (e.g., development of resistance)

• Long-term use of inhaled ciprofloxacin could limit the utility of systemic fluoroquinolones for treatment of severe bacterial exacerbations and pneumonia in NCFB patients
Comments from Advisory Committee

• Time to first exacerbation may not be best primary endpoint; frequency of exacerbations more meaningful
• Consider additional measures: severity of exacerbations, hospitalizations, need for intravenous therapy, total days of antimicrobial therapy, changes in PFTs, quality of life measures
• Duration of trials: one-year trial insufficient duration to evaluate frequency of exacerbations
• Reduce heterogeneity of patient population: standardization of adjunctive therapies, require minimum number of exacerbations for enrollment
• Antimicrobial resistance a major concern that might limit durability of treatment effect and limit utility of parent drug for more severe infections
Outline for Session

• State of the Art in NCFB Care: Greg Tino, MD
• Patient Perspective: Jasan Zimmerman
• Case Study and Discussion
  – Patient Selection: Peter Kim, MD, MS
  – Endpoint Considerations: LaRee Tracy, MA, PhD