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

[1]Am J Respir Crit Care Med 2000;162:481; [2]Ann Pharmacother 2005;39:39; [3]Am J Resp Crit Care Med 2011;183:491

Inhaled Antibacterials in NCFB

- Aztreonam
  - Barker et al.[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.[2]: colistin vs. placebo for up to 6 months (N=144); no significant difference in time to exacerbation; *P. aeruginosa* density reduced at 4 and 12 weeks, SGRQ improved at 26 weeks

[1]Lancet Respir Med 2014;2:738; [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


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