Inhaled Antimicrobial Therapy for CF: A Regulatory Evolution

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Development of Inhaled Antibacterial Treatments for Cystic Fibrosis and Non-Cystic Fibrosis Bronchiectasis

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Approved Inhaled Antimicrobial Products for CF

- TOBI, approved in 1997
  - Several nebulized tobramycin products also approved (Bethkis); TOBI Podhaler approved in 2013
- Cayston (aztreonam), approved in 2010

Drug Development Evolution

– Pathogens targeted

– Drug regimens/combinations

– Endpoints

– Trial Design Considerations

Pathogens

- Initial developmental focus on *Pseudomonas aeruginosa*
- Other CF-associated pathogens being targeted
  - *Staph. Aureus* (MRSA)
  - NTM
  - *Burkholderia* species

Drug Regimens

-Historically

    - singular inhaled drug targeting *Pseudomonas aeruginosa* in 28 Day On/Off cycles

-Currently much more diverse inhaled antimicrobial treatment patterns

    - targeting a variety of pathogens for a variety of purposes (suppression, eradication, etc.)

    - continuous use for *Pseudomonas* (alternating therapies)

    - variety of devices from different manufacturers

Initial Acquisition of *P. aeruginosa* in Patients with Cystic Fibrosis

- Initial acquisition of *P. aeruginosa* in the lungs usually occurs in childhood.
- Affects long term pulmonary disease and survival.
- Higher risk of death than in patients of same age range without *P. aeruginosa*.
- First acquisition of *P. aeruginosa* may be easier to eradicate.

Treatment of Initial Acquisition of *P. aeruginosa* in Patients with Cystic Fibrosis

- Treatment Guidelines from CF Foundation (Moygayzel, 2014).
  - Recommended: Tobramycin inhaled 300mg bid for 28 days.
  - Do not use anti-pseudomonal drugs to prevent acquisition of *P. aeruginosa.*
  - Monitor sputum cultures or oropharyngeal cultures in children unable to expectorate sputum.

Endpoints

- Relative change in FEV 1 % predicted
  - Basis for TOBI approval as well as similar drugs
  - Historically compared to placebo over 1-3 On/Off cycles
  - Important secondary clinical endpoints (hospitalization, time to antimicrobial use, etc.)
- Currently consideration given to other primary endpoints
  - PROs (Cayston)
  - Clinical Events (exacerbations [frequency, time to])
  - Antimicrobial use

Trial Design Considerations

- When can we ask for placebo-controlled trials and for how long?
- How do we ensure the selection of the proper patient population?
- How do we separate the effects of being on multiple therapies?
- Which endpoint best serves a particular trial?
- How long should a particular trial be?