FDA Statistical Perspective

Daniel Rubin, PhD

Division of Biometrics IV, Office of Biostatistics, OTS, CDER, FDA

FDA-IDSA-NIH-Pew Public Workshop

November 19, 2019

Outline

- Endpoints
- Borrowing information across body sites
- Carbapenem-resistant pathogen studies

Endpoints

- Anti-infective registration trials have traditionally used binary primary endpoints where each patient is classified as having experienced success or failure

- Definition of failure varies across indications:
  - Hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP): All-cause mortality
  - Complicated intra-abdominal infections (cIAI): Clinical failure
  - Complicated urinary tract infections (cUTI): Clinical failure or microbiological failure

Endpoints

- Ordinal endpoints could be considered[1] with finer gradations of success:

  Death < Survival with major morbidity < Survival without major morbidity

- Can increase statistical power

- Can provide more informative outcome comparisons

- Levels should be chosen so that treatment differences will not be driven by effects on components with minor clinical importance, or solely by safety, and assigning weights or utilities to outcome categories can be beneficial

- Less data may exist with which to quantify noninferiority margins for use of such endpoints, and they were mainly proposed for superiority trials

Borrowing information across body sites

- Statistical methods such as Bayesian hierarchical models attempt to borrow information across body sites of infection

- Integrated analysis

- Model-based estimates for body site-specific treatment effects can become much less noisy

Borrowing information across body sites

- FDA has used some forms of information borrowing:
  - Supportive evidence for an NDA based on a single successful Phase 3 trial can come from a successful study at another body site of infection
  - Combining of HABP and VABP into HABP/VABP trials
  - Unmet need guidance accepts pooling body sites for superiority trials, and registration trial designs[3] have combined HABP/VABP and bacteremia

- Issues we are likely to take into account when reviewing proposals:
  - Statistical operating characteristics if treatment effects differ across body sites
  - Previous history of discordant results across body sites for some antibacterial drugs (e.g., daptomycin, doripenem, tigecycline)
  - Clinical judgments of heterogeneity between the infection types, pathogens, and endpoints proposed for an integrated analysis

Carbapenem-resistant pathogen studies

- These studies address the questions most closely related to unmet needs

- Large scale enrollment in randomized trials has been very challenging, but achievable in some academic studies[2]

- Historical controls or non-randomized comparisons are limited by the ability to control for confounding in a patient population with many co-morbidities

Carbapenem-resistant pathogen studies

- Borrowing information from studies of carbapenem-susceptible infections to determine efficacy for carbapenem-resistant infections is challenging due to patient differences
  - Could mortality results in the CARE study[3] of plazomicin and CREDIBLE-CR study[4] of cefiderocol have been predicted based on preclinical data and previous results from cUTI noninferiority trials?

- Folding patients with carbapenem-resistant pathogens into new noninferiority trials (with a flexible active comparator choice) would follow the template used for MRSA or ESBLs
  - There may be limited data on the active control used for these patients and risk of noninferiority biocreep[5]

References

1. Evans S et al. Desirability of outcome ranking (DOOR) and response adjusted for duration of antibiotic risk (RADAR). *Clinical Infectious Diseases* 2015;61(5):800-806.
2. Wang J, Niu H, Wang R, and Cai Y. Safety and efficacy of colistin alone or in combination in adults with *Acinetobacter baumannii* infection: a systematic review and meta-analysis. *International Journal of Antimicrobial Agents* 2019;53(4):383-400.
3. https://www.fda.gov/advisory-committees/antimicrobial-drugs-advisory-committee-formerly-known-anti-infective-drugs-advisory-committee/briefing-information-may-2-2018-meeting-antimicrobial-drugs-advisory-committee-amdac
4. https://www.fda.gov/advisory-committees/advisory-committee-calendar/october-16-2019-antimicrobial-drugs-advisory-committee-meeting-announcement-10162019-10162019#event-materials
5. Everson-Stewart S and Emerson SS. Bio-creep in non-inferiority clinical trials. *Statistics in Medicine* 2010;29(27):2769-2780.