Summary Remarks

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Animal Models Workshop
White Oak, March 5, 2020

Animal Model Advances*

- Clinical Relevance
- Interpretability/Reliability
- Points from Discussion

***Previous FDA Workshop:**
"Current State and Further Development of Animal Models of Serious Infections Caused by *Acinetobacter baumannii* and *Pseudomonas aeruginosa*", March 1, 2017

Animal Model Advances

Clinical Relevance

- The natural history of disease in animals informs study design
  - Natural history data provides a rationale for the trigger to treat
  - Some models no longer require immunosuppression to establish bacterial infection
- Use of humanized dosing: Human equivalent exposure of antibacterial drugs in late stage animal models of infection
- Animal model endpoint(s) (e.g. mortality) are aligned with endpoints in clinical trials

Animal Model Advances
Reliability and Interpretability

- The data can be “noisy” and reproducibility remains a challenge
- Some variables are known and can be harmonized
  - Bacterial strain, inoculum size, and route of infection
  - Choice of animal species, genetic background, conditioning
  - Trigger to treat, controls and study endpoints
- Some lessons have been learned along the way
  - Endogenous flora causing co-infection (pig models)
  - Idiopathic drug elimination rates (ciprofloxacin in rabbits, meropenem in mice) or toxicities (doxycycline in AGMs)
- Some important questions remain
  - Work is needed to achieve models that can credibly forecast the results of clinical trials
    - Changes in CFU are a reasonable endpoint, but clinical significance remains unknown
  - The ability to reproduce animal models in different laboratories is untested

Points from Discussion

- Opportunities for improvement: There is more than just CFU as an endpoint. Different models can capture multiple aspects of the clinical disease to be more relevant.
  - Radiology has been underutilized
  - Other variables, such as blood gases, cytokine responses may be useful
- There is no one size fits all model. There are different model requirements depending on the scientific question asked (early dose determination, drug activity against specific strains later in development).
- Challenges remain in the close PK modeling of some antibacterial drugs. New strategies may be needed (i.e. cilastatin with meropenem)

Points from Discussion

- How can we rely on animal data to support an NDA?
  - Performed in tandem with adequate and well-controlled clinical trial(s) to give supporting information (i.e. rare pathogens or certain resistance phenotypes)
  - Use of PK/PD analysis for humanized equivalent exposure
  - Activity demonstrated in multiple animal models with multiple parameters (strains, inoculation sites and sizes)
  - Use of appropriate experimental controls
  - Potential description of the animal studies in product labeling (Microbiology, 12.4)

Upcoming DAI Workshops at FDA

5/7/2020

Development Considerations of Antifungal Drugs to Address Unmet Medical Need

5/8/2020

Developing Antifungal Drugs for the Treatment of Coccidiodomycosis (Valley Fever)

Please refer to FDA Meetings, Conferences and Workshops Page for upcoming workshop and registration details: https://www.fda.gov/drugs/news-events-human-drugs/meetings-conferences-workshops-drugs

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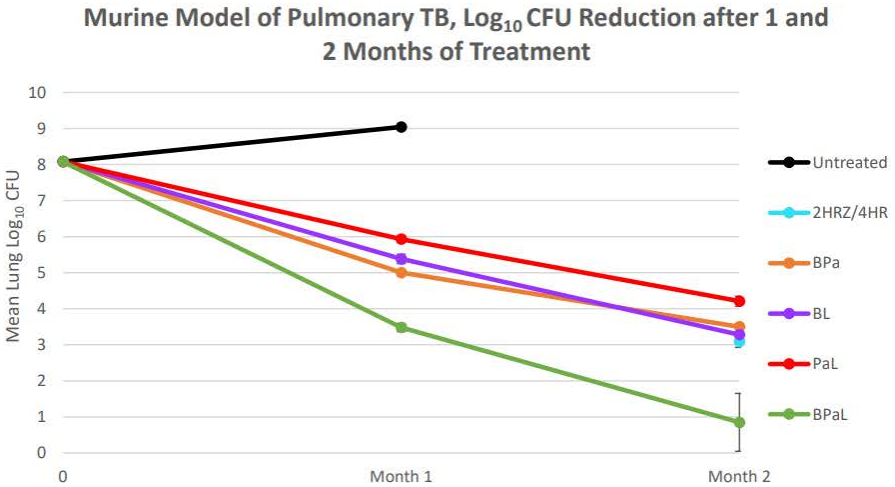
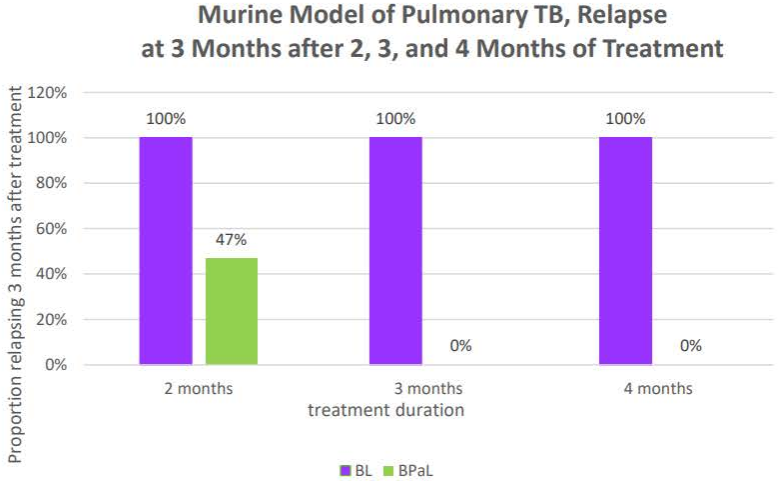
Back Up Slides

Recent Examples of Animal Models Used in Regulatory Decisions (1)

Pretomanid: Use of animal models to demonstrate the contribution of each antibacterial drug in a multiple drug regimen*

- Approved for the treatment of pulmonary extensively drug-resistant and treatment-intolerant/nonresponsive multidrug-resistant tuberculosis in combination with bedaquiline (B) and linezolid (L)
- A clinical trial of pretonamid (Pa) with a factorial design would not have been feasible





Source: https://www.fda.gov/media/128000/download

*Required by the combination drug rule (21 CFR 300.50)

Recent Examples of Animal Models Used in Regulatory Decisions(2)

Cefiderocol Product Labeling

- For treatment of complicated urinary tract infections (cUTI), including pyelonephritis caused by susceptible Gram-negative microorganisms in adult patients who have limited or no alternative treatment options.
- Supportive data in the New Drug Application (NDA) included explorations of animal models (e.g. pyelonephritis, sepsis) with a variety of pathogens and resistance phenotypes.

12.4 Microbiology

Activity against Bacteria in Animal Infection Models

In an immunocompetent murine urinary tract infection model, cefiderocol reduced bacterial counts in the kidneys of mice infected with Enterobacteriaceae, and *P. aeruginosa* isolates with MICs ≤ 1 mcg/mL. In an immunocompromised murine systemic infection model, cefiderocol increased survival in mice infected with *E. cloacae*, *S. maltophilia*, and *Burkholderia cepacia* isolates with MICs ≤ 0.5 mcg/mL compared to untreated mice. In an immunocompetent murine systemic infection model, cefiderocol increased survival in mice infected with *S. marcescens* and *P. aeruginosa* isolates with MICs ≤ 1 mcg/mL compared to untreated mice. The clinical significance of the above findings is not known.

Source: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/209445s000lbl.pdf