Lessons Learned in Animal Model Development: Inhalational Anthrax

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Disclosure Statement: Battelle is a non-profit organization that provides contracted research services to numerous government and commercial Sponsors. The speaker has no financial conflicts of interest.
The Unmet Medical Need

• Developing Medical Countermeasures (MCMs) against anthrax

  ▪ Vaccines
    - BioThrax (AVA)
    - rPA
    - Spore coat proteins

  ▪ Antimicrobials
    - Traditional
    - Novel

  ▪ Antibody Passive Protection
    - mAbs
    - Immune globulin

  ▪ Treatment Indication
    - GUP, PEP, Tx
Understanding the Mechanisms of Pathology
Modeling Therapeutic Treatment (Tx)

**Products:** Monoclonal Antibodies, Polyclonal Antibodies, Antimicrobial Agents

**Requirements:**

- Define the disease
  - Clinical signs of illness – non-specific indicators
  - Diagnostics – specific indicators
- Mimic the clinical scenario
  - Clinical presentation
  - Appropriate timing of MCM intervention
  - Our understanding of clinical scenario is based on historical outcomes of Sverdlovsk release in 1979 and 2001 Amerithrax cases
Defining the Disease

Comer et al. Clinical and Vaccine Immunology. 2012 Sep; 19(9) 1517-1525
**Clinical Profile of Inhalational Anthrax**

**Unchallenged**

**Challenged**

### Next Steps
- Demonstrate anthrax antitoxin treatment following confirmation of disease is effective
- Evaluate the PK of antitoxin in the context of the disease

### Constraints
- Traditional diagnosis was impractical – “surrogate” Dx assay was required.
- Limitations in data collection – prioritizing data type was necessary.
Raxibacumab – Demonstrating Effectiveness

- Median Predicted Human Serum Raxibacumab
- 90% Prediction Interval, Human Serum Raxibacumab
- Observed Rabbit Maximum Serum PA (at death)
- Observed Monkey Maximum Serum PA (at death)

Survival Probability vs. Time (days)

- p = 0.0034 vs. placebo
- p = 0.0181 vs. placebo

Serum Raxibacumab or PA Concentration vs. Time Post Raxibacumab Dose (days)

- 28 days
- 48 days

Placebo

- TX

Clinical Relevance – Added Benefit

Goal
- Demonstrate anthrax antitoxin adds benefit to antimicrobial treatment alone

Constraints
- Marginal (~50%) outcome following treatment with antibiotic
- “Humanized” dosing of antibiotic
- Statistically significant difference between outcome observed following treatment with antibiotic and antitoxin when compared to treatment with antibiotic alone

Design Considerations
- Antibiotic dose
- Antibiotic duration
- Treatment intervention time
Clinical Relevance – Added Benefit

1) Not Therapeutic dosing
2) Dose close to “humanized”
3) Outcome observed after cessation
4) Added benefit observed

Levofloxacin
n=37

Survival (%)

64.9

Raxibacumab/Levofloxacin
n=39

82.1

p=0.0874

www.fda.gov; Corey et al. Toxins 2013, 5(1), 120-138
Summary

• Historical data was the foundation of optimizing the models utilized to assess efficacy.
• Indication dictated development pathway.
• Many iterations were required prior to “final” model
• Quality Management System is critical to successful regulatory review
• Collaborative effort was key and critical to the success of the program
Acknowledgements

• Battelle
  ▪ Aerosol Team
  ▪ Lead Technicians and Staff
  ▪ PA ECL Staff
  ▪ PA ELISA Staff
  ▪ ELISA and TNA staff
  ▪ qPCR Staff
  ▪ Clinical Pathology Staff
  ▪ Analytical Chemistry
  ▪ Pathology Staff
  ▪ Biostatisticians
  ▪ Quality Assurance Staff
  ▪ Facility Staff
  ▪ Study Directors

• USG agencies
  – NIAID
  – BARDA
  – FDA
  – CDC

• Product Sponsors