Developing an Animal Model of Pneumonic Plague

FDA Workshop
March 1, 2017
Disclaimer

- I am a federal employee.
- I receive no external funding.
- I am presenting only federally funded work.
- My opinions are mine and do not necessarily represent those of the NIAID/NIH.
Pneumonic Plague Treatment Efficacy of Two Fluoroquinolones
sNDA Submission: 400 MB, >250 files

4 NHP natural history
1 NHP efficacy
4 NHP pathology/radiology
3 NHP PK
2 assay validation
2 small animal efficacy
2 in vitro MIC
18 reports

79%: 18 reports, 64 refs, datasets
19%: 1 white paper, 70 refs
### African Green Monkey (AGM) Natural History Studies

<table>
<thead>
<tr>
<th>Study, Site</th>
<th>Number of Animals</th>
<th>Challenge Dose, LD$_{50}$</th>
<th>Mean Time to Death, hours</th>
<th>Mortality # Bacteremic/# Febrile</th>
</tr>
</thead>
<tbody>
<tr>
<td>F03-09G, USAMRIID</td>
<td>3 M, 3 F</td>
<td>25.3 ± 17.3</td>
<td>111.8 ± 10.4</td>
<td>4/6 4/4</td>
</tr>
<tr>
<td>FY06-126, Lovelace</td>
<td>5 M, 5 F</td>
<td>134.7 ± 68.1</td>
<td>90.1 ± 10.0</td>
<td>10/10 10/10</td>
</tr>
<tr>
<td>617, Battelle</td>
<td>3 M, 7 F</td>
<td>613.7 ± 386.1</td>
<td>72.8 ± 11.1</td>
<td>10/10 10/10</td>
</tr>
<tr>
<td>875, Battelle</td>
<td>5 M, 5 F</td>
<td>48.1 ± 23.1</td>
<td>93.3 ± 21.3</td>
<td>10/10 10/10</td>
</tr>
<tr>
<td>Overall</td>
<td>36 (16 M, 20 F)</td>
<td></td>
<td></td>
<td>34/36 (94%) 34/34</td>
</tr>
</tbody>
</table>
# Bacteremia

<table>
<thead>
<tr>
<th>Animal</th>
<th>Inhaled Dose, LD&lt;sub&gt;50&lt;/sub&gt;</th>
<th>24</th>
<th>48</th>
<th>72</th>
<th>80</th>
<th>83</th>
<th>96</th>
<th>Terminal cfu/ml (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>V627</td>
<td>57</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>nd</td>
<td>+</td>
<td>+</td>
<td>8x10&lt;sup&gt;7&lt;/sup&gt; (111.5)</td>
</tr>
<tr>
<td>V514</td>
<td>30</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>nd</td>
<td>+</td>
<td>3x10&lt;sup&gt;6&lt;/sup&gt; (111)</td>
</tr>
<tr>
<td>V569</td>
<td>23</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>nd</td>
<td>+</td>
<td>+</td>
<td>9x10&lt;sup&gt;8&lt;/sup&gt; (99.5)</td>
</tr>
<tr>
<td>V113</td>
<td>21</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>nd</td>
<td>+</td>
<td>+</td>
<td>1x10&lt;sup&gt;8&lt;/sup&gt; (125)</td>
</tr>
<tr>
<td>V521</td>
<td>12</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>nd</td>
<td>nd</td>
<td>-</td>
<td>nd</td>
</tr>
<tr>
<td>V605</td>
<td>9</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>nd</td>
<td>nd</td>
<td>-</td>
<td>nd</td>
</tr>
</tbody>
</table>

+ = growth; - = no growth; nd = not done
Body Temperature, Survivor vs. Non-Survivor

The graph shows the body temperature over time for two groups: Survivor and Non-Survivor. The Temperature in °C is plotted against Hours Post-Challenge. The Survivor group is represented by blue line (V521), and the Non-Survivor group by red line (V113). The temperature fluctuates significantly, with the Survivor group generally maintaining a lower temperature than the Non-Survivor group, indicating a potential difference in their response or condition.
Heart Rate, Survivor vs. Non-Survivor

Heart Rate, beats per minute

Hours Post Challenge

- V521
- V113
Respiratory Rate

![Graph showing respiratory rate over time for different individuals labeled V627 (M), V514 (F), V569 (M), V605 (M), V113 (F), and V521 (F). The x-axis represents hours post challenge, and the y-axis represents breaths per minute.]
Chest Radiographs

0 hr  83 hr  111.5 hr
Individual Animal Endpoint Profile

Respiratory Rate

Heart Rate

Temperature
Survival, across Studies

- USAMRIID Natural History
- Lovelace Natural History
- Battelle Natural History (1000 LD50)
- Battelle Natural History
Bacteremia, across Studies

Day 1 | Day 2 | Day 3 | Day 4

- USAMRIID F03-09G
- Battelle 875
- Lovelace FY06-126
- Battelle 617
Time to Death by Challenge Dose

- USAMRIID
- Lovelace
- Battelle-617
- Battelle-875

Time to Death (hours)

LD50
Mean Time from Fever to Death

- USAMRIID F03-09G: 32.8 LD<sub>50</sub>
- Lovelace FY06-126: 134.7 LD<sub>50</sub>
- Battelle 617: 613.7 LD<sub>50</sub>
- Battelle 875: 48.1 LD<sub>50</sub>
## Lung Pathology – Incidence of Findings

<table>
<thead>
<tr>
<th></th>
<th>F03-09G (4)</th>
<th>FY06-126 (10)</th>
<th>617 (10)</th>
<th>875 (10)</th>
<th>TOTAL (34)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacteria</strong></td>
<td>4</td>
<td>9</td>
<td>10</td>
<td>10</td>
<td>33</td>
</tr>
<tr>
<td><strong>Edema</strong></td>
<td>3</td>
<td>6</td>
<td>10</td>
<td>10</td>
<td>29</td>
</tr>
<tr>
<td><strong>Hemorrhage</strong></td>
<td>4</td>
<td>10</td>
<td>8</td>
<td>9</td>
<td>31</td>
</tr>
<tr>
<td><strong>Inflammatory infiltrate, intra-alveolar, macrophage</strong></td>
<td>4</td>
<td>10</td>
<td>10</td>
<td>6</td>
<td>30</td>
</tr>
<tr>
<td><strong>Inflammatory infiltrate, intra-alveolar, neutrophil</strong></td>
<td>4</td>
<td>10</td>
<td>10</td>
<td>6</td>
<td>30</td>
</tr>
<tr>
<td><strong>Necrosis, multifocal</strong></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td><strong>Pleura, fibrin</strong></td>
<td>3</td>
<td>10</td>
<td>3</td>
<td>8</td>
<td>24</td>
</tr>
<tr>
<td><strong>Pleura, inflammatory infiltrate, macrophage</strong></td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Within normal limits</strong></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Human Plague in the Modern Era

1855 – present
- China (1855)
- Russia (1877 – 1889)
- Hong Kong (1894)
  - Dr Yersin discovers bacterium
- Venice conference to keep Europe
- Hawaii (1899)
  - declared eradicated in 1959
- San Francisco (1900)
- Galveston (1920)
- Los Angeles (1924) 30 deaths (pneumonic)
- Surat, India (1994) 52 deaths (pneumonic), 300K migration
- Congo (2006) ~100 deaths (pneumonic)
# Disease Comparison

<table>
<thead>
<tr>
<th>Disease Feature</th>
<th>Human</th>
<th>AGM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time course, days</td>
<td>2 to 9</td>
<td>2 to 9</td>
</tr>
<tr>
<td>Temperature</td>
<td>Elevated in 100% of cases</td>
<td>Elevated in 100% of cases</td>
</tr>
<tr>
<td><em>Y. pestis</em> present</td>
<td>Positive in 100% of sputum</td>
<td>Positive in 100% of blood and/or lung/nasal fluid</td>
</tr>
<tr>
<td>Heart rate</td>
<td>Elevated</td>
<td>Elevated</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>Elevated</td>
<td>Elevated</td>
</tr>
<tr>
<td>Chest radiograph</td>
<td>Pulmonary infiltrates, 90% bilateral</td>
<td>Pulmonary infiltrates, 65% bilateral</td>
</tr>
<tr>
<td>Pathology, lung</td>
<td>Consolidations, Inflammatory infiltrates, Hemorrhagic/frothy fluid, Exudates and effusions, Bronchopneumonia, Bacilli</td>
<td>Bacteria, Edema, Hemorrhage, Inflammatory infiltrates, Bronchopneumonia, Pleural fibrin</td>
</tr>
</tbody>
</table>
Bridging from animals to humans

Animal PK

Animal Efficacy

Human PK

??

Human Efficacy

??
Lessons Learned

- Talk to FDA early about selection of animal model and correlation to human disease
- Standardize methods & reagents as early as possible
- Quality is extremely important
- Pharmacokinetics are extremely important
  - Establish SOPs
  - Use validated assays
  - Be careful with blood volumes and repeat assays
  - Draw blood samples from a different port/site than dosing
- Pivotal animal rule studies replace Phase III clinical trials for efficacy
Requirements of Animal Models for Animal Rule Studies

- Need to understand the human disease
  - Route of infection
- Develop animal model
  - Identify relevant strain, characterize, develop master & working bank
  - Select one or more species most relevant to humans
  - Collect data to identify relevant endpoints
  - Establish reproducibility of model
- Proof of concept for intervention (e.g., trigger to treat)
- Selection of an effective dose
- Quality systems to support efficacy testing of drugs (GLP, 21 CFR 58)
# Generic GLP Challenge/Efficacy Study Timelines

<table>
<thead>
<tr>
<th>Stage</th>
<th>Rodent</th>
<th>Rabbit</th>
<th>NHP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animal Protocol Development</td>
<td>1 months</td>
<td>1 month</td>
<td>1-2 months</td>
</tr>
<tr>
<td>Animal Order, Receipt</td>
<td>2 weeks</td>
<td>0.5-1 month</td>
<td>2 months</td>
</tr>
<tr>
<td>Quarantine</td>
<td>1 week</td>
<td>1 week</td>
<td>1-1.5 months</td>
</tr>
<tr>
<td>Pre-study Surgery/Recovery</td>
<td>0-1 month</td>
<td>0-1 month</td>
<td></td>
</tr>
<tr>
<td>Pre-study Acclimation/Baseline</td>
<td>1 week</td>
<td>1 week</td>
<td>0.5-1 month</td>
</tr>
<tr>
<td>In-Life</td>
<td>1 month</td>
<td>1-2 months</td>
<td>1-2 months</td>
</tr>
<tr>
<td>Sample processing/Pathology</td>
<td>1-2 months</td>
<td>3-4 months</td>
<td>4-5 months</td>
</tr>
<tr>
<td>QC Data Review/QAU Auditing/Statistical Analysis</td>
<td>1 month</td>
<td>2-3 months</td>
<td>3-4 months</td>
</tr>
<tr>
<td>Draft Report</td>
<td>1 month</td>
<td>2-3 months</td>
<td>2-3 months</td>
</tr>
<tr>
<td>Final Report</td>
<td>0.5 month</td>
<td>1-2 months</td>
<td>1-2 months</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>6.5-7.5</strong> months</td>
<td><strong>11-17</strong> months</td>
<td><strong>15-24</strong> months</td>
</tr>
</tbody>
</table>
"Enough with the low-hanging fruit. How about some slow-moving meat?"
BACKUP SLIDES
The Animal Efficacy Rule

FDA may grant marketing approval for a new drug product for which safety has been established and for which the requirements of 314.600 are met based on adequate and well-controlled animal studies when the results of those animal studies establish that the drug product is reasonably likely to produce clinical benefit in humans. In assessing the sufficiency of animal data, the agency may take into account other data, including human data, available to the agency. FDA will rely on the evidence from studies in animals to provide substantial evidence of the effectiveness of these products only when:

1. There is a reasonably well-understood pathophysiological mechanism of the toxicity of the substance and its prevention or substantial reduction by the product;
2. The effect is demonstrated in more than one animal species expected to react with a response predictive for humans, unless the effect is demonstrated in a single animal species that represents a sufficiently well-characterized animal model for predicting the response in humans;
3. The animal study endpoint is clearly related to the desired benefit in humans, generally the enhancement of survival or prevention of major morbidity; and
4. The data or information on the kinetics and pharmacodynamics of the product or other relevant data or information, in animals and humans, allows selection of an effective dose in humans.

21 CFR 314.600
21 CFR 601.90
The Need for the Animal Rule

- DoD desired drugs for biothreats against soldiers in Operation Desert Shield/Storm (1990-1) for anthrax, plague, chemical weapons
- USAMRIID studied ciprofloxacin, penicillin, doxycycline (+ vaccine) for anthrax prophylaxis in NHPs (Friedlander et al, JID 167:1239, 1993)
- Cipro was approved by FDA 8/30/2000
  - Transcripts (7/28) [http://www.fda.gov/ohrms/dockets/ac/cder00.htm#Anti-Infective](http://www.fda.gov/ohrms/dockets/ac/cder00.htm#Anti-Infective)
- Cipro approval used a surrogate endpoint under Subpart H, “Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses” (21CFR314.500)
- FR notice for doxy & pen published 11/2/2001
History of the Animal Rule

• 10/5/1999: FR notice proposing the Animal Rule
  • Comment period closed 12/20/1999


• “On the Origin of the Animal Rule” (7/7/2010)

• “FDA Experience with Medical Countermeasures under the Animal Rule” (7/21/2011)
  • [https://www.hindawi.com/journals/apm/2012/507571/](https://www.hindawi.com/journals/apm/2012/507571/)
Animal Rule Guidance Documents

• Final “Product Development Under the Animal Rule” Guidance issued October 2015.
  
  
  • Public meeting held in November 2010

  
  
  • Website published January 2012
# Animal Efficacy Rule Approvals to Date

<table>
<thead>
<tr>
<th>Date</th>
<th>Drug</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>Pyridostigmine Bromide</td>
<td>For military personnel exposed to Soman nerve gas</td>
</tr>
<tr>
<td>2006</td>
<td>Cyanokit (hydroxycobalamin) *</td>
<td>For cyanide poisoning</td>
</tr>
<tr>
<td>2012</td>
<td>Levaquin *</td>
<td>For treatment of pneumonic plague</td>
</tr>
<tr>
<td></td>
<td>Raxibacumab</td>
<td>For treatment of inhalational anthrax, along with antibiotics</td>
</tr>
<tr>
<td>2013</td>
<td>Botulism Antitoxin Heptavalent (Equine)</td>
<td>For treatment of botulism</td>
</tr>
<tr>
<td>2015</td>
<td>Ciprofloxacin *</td>
<td>For treatment of pneumonic plague</td>
</tr>
<tr>
<td></td>
<td>Anthrasil (anthrax immune globulin)</td>
<td>For treatment of inhalational anthrax, along with antibiotics</td>
</tr>
<tr>
<td></td>
<td>Neupogen (filgrastim) *</td>
<td>For treatment of Hematopoietic Syndrome of Acute Radiation Syndrome</td>
</tr>
<tr>
<td></td>
<td>Moxifloxacin *</td>
<td>For treatment of pneumonic plague</td>
</tr>
<tr>
<td></td>
<td>Neulasta (pegfilgrastim) *</td>
<td>For treatment of myelosuppression after radiologic/nuclear incident</td>
</tr>
<tr>
<td></td>
<td>BioThrax (vaccine)</td>
<td>For post-exposure prophylaxis of anthrax, with antibiotics</td>
</tr>
<tr>
<td>2016</td>
<td>Oblitoxaximab (Anthim)</td>
<td>For treatment of inhalational anthrax, along with antibiotics, and prophylaxis when alternative therapies are not available/appropriate.</td>
</tr>
</tbody>
</table>

* Drugs approved with a single animal model

*italics* = new drug
1. Please comment on the similarities and differences between the African Green Monkey animal model of pneumonic plague and human disease with regard to:
   
   a. Signs and symptoms
   
   b. Outcome
   
   c. Histopathology

2. Discuss the manifestations of pneumonic plague that could be used as a trigger for therapeutic intervention in the African Green Monkey animal model and their relevance to treatment of human disease.
4/2012 Drug Approval Discussions

- The AdCom votes for cipro and levo were unanimous for approval
- Discussed:
  - Small animal models
  - Recent human outbreaks
  - Other markers of disease
  - Statistics and power
  - A single animal model
  - Immediate treatment