Anthrax Therapeutics: The Role of BARDA in the Development of Anthrax Medical Countermeasures

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Overview

• Background
• Available Therapeutics
• USG Strategy for anthrax MCMs
• Development of anthrax antitoxins
• Licensure under the Animal Rule
• Future of anthrax MCMs
• Working with BARDA
Background

• Causative agent –
  Gram positive bacterium *Bacillus anthracis*

• Three clinical forms of the disease:
  – Cutaneous, gastrointestinal, inhalational

(Images: CDC and Imageinvision.com)
Background

• Currently Project Bioshield anthrax therapeutics’ INDs are for the indication of inhalational anthrax

• Inhalational anthrax clinical manifestations and timelines:
  ─ 4-14 day incubation, but spores may last for months in lungs
  ─ 2-3 day prodrome—fever, malaise (non-specific)
  ─ Death occurs rapidly without supportive care

• Not readily transmitted from person to person

• Three treatments available:
  antibacterials, vaccines, antitoxins

• All three treatments part of USG strategy for preparedness and response
Available Therapeutics

• Two types of antitoxins available

  - Monoclonal antibodies produced by mammalian cell culture

  - Polyclonal antibodies produced from human plasma after vaccination

  ❖ Anthrax Immune Globulin (AIG) is a polyclonal anthrax antitoxin therapeutic manufactured by Cangene Corporation.

  ❖ Raxibacumab is a monoclonal anthrax antitoxin therapeutic manufactured by Human Genome Sciences, Inc. (HGS)
Available Therapeutics

• Both AIG and Raxibacumab:
  - Are not yet licensed
  - Have an IND held by CDC
  - Have Pre-EUA packages submitted by CDC to FDA (CBER and CDER)

• Antitoxins have been used
  - Three cases associated with African drums in US
  - The polyclonal antitoxin (AIG) was used to treat naturally-occurring cases of anthrax in both the US and the UK
  - In UK fifteen cases associated with contaminated heroin (over fifty cases total)
  - AIG used in all cases under CDC held IND
USG Strategy

• Establish antitoxin requirements
  — Completed: two requirements
  — Treatment courses for drug sensitive anthrax
  — Treatment courses for drug resistant anthrax

• Fulfillment of requirements
  — Acquisition of products via Project BioShield contracts
  — Development of products via Advanced Research and Development contracts
  — Review portfolio as requirements change
  — Maintain pipeline until licensed products available
USG Strategy

• Acquisition Strategy

  – Near term- fulfill requirements with technologies immediately available, acquisitions based on fit between technology and concept of operations (antibody-based antitoxins)

  – Mid-term- improve technologies immediately available (improved ease of administration, formulation, stability)

  – Long term- investment in next generation technologies (small molecule antitoxins)
• PBS acquisition contract with Human Genome Sciences, Inc. for up to 100,000 treatment courses of raxibacumab
  — Base award for 20,001 treatment courses
  — Options exercised for 45,000 additional treatment courses
  — To date, ~49,000 doses of raxibacumab delivered to SNS

• PBS acquisition contract with Cangene Corporation for up to 100,000 treatment courses of Anthrax Immune Globulin (AIG)
  — Base award for 10,000 treatment courses
  — To date, 10,000 doses of AIG delivered to SNS
Anthrax Therapeutics Contract Summary

- Seven contracted companies developing anthrax therapeutics in varying stages of development

- All contracts funded by BARDA; some contracts managed by NIAID

- Two companies currently delivering product to the SNS (1 polyclonal and 1 monoclonal)
  - 2 polyclonal therapies; all polyclonals stored at -20°C
  - 5 monoclonal therapies; all monoclonals stored at 2-8°C
Animal Rule Licensure

- Clinical trials with anthrax not feasible
- Safety demonstrated in humans

- Efficacy demonstrated in animal models
  - NOT “Two Animal Rule”
  - Small animal model for “statistical data”
  - Large animal model for bridging correlates or surrogates
  - Models must be accepted before pivotal studies possible
    - Model reflect the disease in humans
    - Treatment predict human response

- Identify human dosage
  - Evaluate repeat-dose safety
Additional Issues to Consider

• Concomitant use of other MCMs
  — Vaccines, antivirals, antibacterials
• Anthrax antitoxins will be used with antibacterials
  — FDA requires demonstration of “added benefit” before approval
  — Development of antibacterial treatment model required
  — All three models- monotherapy, antibacterial, and combination therapy- must be accepted by FDA
  — Antibacterial treatment model must reflect results of use in humans
• Antibacterials have a label indication for use as Post Exposure Prophylaxis only.
Model Expectations

• Antibacterial model parameters established by FDA
  – Antibacterial dosage - full human equivalent
  – Treatment initiation - clinically relevant data
  – Treatment duration - five days minimum

• Model goal
  – 50% survival of animals treated with antibacterial alone
  – Defined added benefit in combination treatment groups
  – Statistical significance required
Sponsor Consortium

• USG funding development of multiple products to mitigate risk
• Each sponsor required to demonstrate added benefit
• Inefficient for USG to fund parallel development of several models independently
• Inefficient use of limited model development and testing resources
• All USG-funded sponsors participating in consortium
  — Control data from studies pooled for meta-analysis
  — Effort started spring 2010, first report expected this spring
  — Correlation with human data if possible
Future of Anthrax Therapeutics

• Address gaps in advanced development portfolio

• Targets
  ─ All antitoxins in advanced development target Protective Antigen
  ─ Solicit white papers/proposals regarding antibody-based antitoxins based on other targets (lethal factor, edema factor)

• Administration and storage
  ─ All antitoxins in advanced development administered as IVs
  ─ Solicit white papers/proposals for improved formulation, alternate administration routes, storage without cold-chain
Future of Anthrax Therapeutics

• All antitoxins in advanced development based on antibodies (monoclonal/polyclonal)
  
  – Solicit white papers/proposals regarding small molecule antitoxins or antidotes
  
  – Keep in mind TRL requirements: must have active IND and initiated clinical trial
Interfacing with BARDA

• www.phe.gov
  — Program description, information, news, announcements

• www.medicalcountermeasures.gov
  — Portal to BARDA
  — Register, request a meeting
  — Tech Watch

• www.fedbizopps.gov
  — Official announcements and detailed information about all government contract solicitations