Tuberculosis Vaccines

FDA Perspective on Phase 2 Clinical Trials

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Tuberculosis Vaccine Development Phase 2 Trials

- Goals
  - Safety
  - Immunogenicity
  - Dose-finding
  - Adjuvants

Trial Design Issues

- Logistics
- Population
- BCG and live vaccine issues
- Strategies
- Endpoints
- Safety

Trial Logistics

- Location
  - Epidemiology/ incidence of disease
  - Infrastructure/refining protocol procedures
- Duration and follow-up
- Trial size (50-500 subjects)
- Challenges regarding endpoints
  - diagnostic tests
  - case definitions for latent TB infection and active TB disease

Study Population

- Immunocompetent adults
  - No evidence of latent or active TB infection (PPD negative vs QFT)
  - Not a BCG recipient
- Sensitized immunocompetent adult
  - BCG recipient
  - PPD positive (not a recent converter who warrants INH therapy and no active TB)

Study Population

If ultimate goal is to evaluate study vaccine in a highly TB endemic area (which may also be HIV endemic) in un-sensitized individuals such as neonates-----how is this done safely?

What safety (and efficacy) data is required prior to enrolling infants?

What data is required prior to studying a new vaccine in an HIV positive population?

Issues regarding BCG

- Efficacy
- Ethics of withholding BCG
- Different strains-standardize comparators
- Different methods of administration
- Infrastructure for administration in place
- Impact on trial design –BCG comparator

Live TB Vaccine Risks

- Dissemination
  - Concern for study population with HIV
- Resistance
  - INH
  - Antibiotic resistance markers
- PPD reactivity
  - loss of PPD as surveillance tool

Prime-Boost Strategy

- If study subjects receive BCG as infants ("BCG prime")---will need to provide a rationale for when to administer the study vaccine "boost" considering:
  - When is the most immunologically feasible time to boost with study vaccine?
  - When is the most practical time to boost with study vaccine e.g. at time of entry to elementary school ?

Immunogenicity Endpoints

- CMI
- Humoral immunity
- Validate assays
- Response to PPD
  - Significance and correlation with other parameters of immunogenicity and efficacy?

Safety Endpoints

- Product specific
- Local and systemic reactogenicity
- Laboratory tests
- Challenges
  - Monitor for dissemination of vaccine strain vs acquisition of TB infection/disease
  - Evaluate fever, weight loss, cough, headache in countries endemic for malaria, dengue, etc.

Efficacy Endpoints in Phase 2

- Tuberculin conversion as a measure of efficacy ?
- Decrease in incidence of TB infection
  - How do we measure this?
- Decrease in incidence of cases of active TB
  - Case definition
  - Field trials required

Special Considerations in Vulnerable Populations

- Informed consent
  - outlining risk of administering live vaccines
- Withholding BCG
  - may not be ethical, even in country with BCG failures
- Safe progression from healthy adult clinical trial population to children

Conclusions

- Challenges of developing a TB vaccine
- Early phase studies need to support the efficacy
- Path to licensure may be different depending on the epidemiology of TB in the country of interest
- Field efficacy trials required
- Advisory Committee option