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Drug Z-4: Hypothetical Case of a Chimeric Bacteriophage Endolysin

Edward Weinstein, MD, PhD

Division of Anti-Infective Products
Office of Antimicrobial Products

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Overview of Drug Z-4

- Recombinant chimeric protein (30 kD) comprised of ectolysin domain from a bacteriophage enzyme fused to a *Staphylococcus* binding domain of bacterial origin.

- Development program intended to treat *Staphylococcus aureus* skin infections via topical administration, and endocarditis via intravenous infusion.

- No activity against other Gram-positive or Gram-negative bacterial species.

Nonclinical Safety

- Rats, Mini-pigs: Intravenous administration was tolerated at doses up to 5 times the proposed human equivalent when administered daily for two consecutive weeks. No dose limiting toxicity.
- Transient fevers of less than 24 hours duration noted in some animals
  - Endotoxin contamination suspected. Drug substance is produced by batch fermentation of *E. coli* cultures
  - Anti-drug antibodies identified in rats at day 28
  - Perivascular neutrophilic infiltrates noted at injection site. Significant toxicity in related ectolysins include severe, irreversible vasculitis due to off-target activity.
- In mice & rabbits, a topical solution at the proposed clinical dose was applied to abraded skin daily for 14 days without significant toxicity.

Nonclinical Microbiology

- Drug Z-4 is only active vs. *Staphylococcus spp (S. aureus* and coagulase-negative species [CONS])

- MICs follow a normal distribution for *S. aureus* (MIC range 0.03 – 16 mg/L; MIC_{90} 8 mg/L). No overt resistance noted in screening panel

- Time-kill: 4-log reduction in MRSA USA300 counts following 15 minutes exposure at 4x MIC concentration *in vitro*
  - Insufficient data to establish a pharmacodynamic model

Nonclinical Microbiology & PK/PD

- The predicted PK/PD properties associated with bacterial killing:
  - A linear relation between killing and drug concentration is anticipated, with a mode of action characterized by irreversible binding to target.

- In animal infection models, Drug Z-4 was effective in treating *S. aureus* infections
  - Based on reduction of CFU/g: thigh and peritonitis models
  - Based on survival: peritonitis

Clinical Studies

- Phase 1A and Phase 1B studies completed

- Phase 1A:
  - 24 healthy volunteer, single and multiple dose nasal ointment at the proposed dose (1% by weight).
    - In general, Drug Z-4 was well tolerated. No discontinuations or serious adverse events reported.
    - One subject with transient fever 4 hours after administration.

Phase 1B Proof of Concept Study

- Open label study conducted in 20 healthy patients with MRSA nasal colonization.
- Drug Z-4 ointment was given topically TID at several doses (placebo, 0.1%, 0.3%, 1.0% w/w) x 5 days.
- Study endpoint was daily quantitation of MRSA by lavage from nares 30 minutes before, 30 minutes after and 4 hours following evening application.
- The only efficacy analysis which displayed a significant difference between drug and placebo in *S. aureus* clearance was in the 1% dose group 30 minutes after drug administration; this difference disappeared at the 4 hour time point on day 1.
- One adverse event (AE) of fever and leukocytosis 4h post administration on Day 5. No other AEs of concern observed. Drug not detected systemically, but one subject was positive for anti-Z-4 antibodies at Day 20.

Questions for the panel…

- **Clinical trial design**. Which indication(s) and patient population(s) should be recommended for a clinical trial involving a single-course, single-genus therapy? Would a trial be feasible if enrollment is limited to the pathogen(s) of interest and outcomes are confounded by the administration of effective, empiric therapy?
- **Safety**. Given the potential immunogenicity of a drug derived from foreign proteins, how would you ensure that a patient would receive a limited exposure? Would you screen for the presence of anti-drug antibodies?