Drug X-1: Hypothetical case of a monoclonal antibody for prevention of a bacterial disease

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Nontraditional Therapies Workshop

August 21, 2018

Overview of Antibody X-1

- Injectable humanized immunoglobulin IgG1κ
- Exogenous target
- Binds specifically to the alpha toxin (AT) of *Staphylococcus aureus*, blocking AT pore formation in target cell membranes and protecting cells from lysis
- Narrow spectrum, no activity against other pathogens
- Prevention of ventilator-associated bacterial pneumonia by *S. aureus*

Nonclinical studies

- In a murine model of pneumonia, prophylaxis with a murine version of the product reduced disease severity with an EC_{90} of 200 µg/mL.
- Repeat dose (2-week duration) toxicology study in rats – no toxicity identified
- 6-week repeat dose toxicity study in monkeys - immune complex arteritis
- Tissue cross-reactivity study- negative (no staining)
- Crossed placenta - reproductive toxicity studies conducted
- Single-dose pharmacokinetic study in monkey - positive antidrug antibodies

Clinical pharmacology

- Phase 1 first-in-human study completed
- Terminal half-life of 90-110 days
- Serum concentrations maintained above the PK target for 30 days
- Clinical immunogenicity – 5% subjects tested positive for ADA during the study
- 35% developed infusion reactions

Clinical Studies

Phase 2 dose-ranging study in ventilated subjects colonized with *S. aureus* in the lower respiratory tract completed

- Primary efficacy endpoint was incidence of *S. aureus* pneumonia during the 30 days post dosing
- PK analysis showed half life of 40 days, lower than healthy subjects, clearance higher in patients
- A dose of 4000 mg achieved the PK target, which was a serum concentration of 200 mcg/mL
- Antibody concentration in tracheal aspirate measured
- Adverse events of urticaria and rash reported
- One case of laryngeal edema reported – possible hypersensitivity reaction

Clinical Studies

Phase 3 randomized, double-blind placebo-controlled superiority trial (N=582) in ventilated subjects colonized with *S. aureus* in the lower respiratory tract completed

Inclusion criteria:

- Tracheal or bronchial sample positive by polymerase chain reaction (PCR) for *S. aureus* within 36 hours prior to randomization
- No diagnosis of new-onset pneumonia within 72 hours prior to randomization

Phase 3 Clinical Study

Efficacy: Primary efficacy endpoint was incidence of *S. aureus* pneumonia during the 30 days post dosing (clinical symptoms/signs and microbiological culture)

Secondary efficacy endpoint - All cause mortality at day 28

Safety : Adverse events assessed through 30 days post dose, 90 days post dose and 190 days post dose

Results: Incidence of pneumonia in the treatment group was 68/291 (23.4%) compared to 87/291 (29.9%) in placebo group

Difference in rates: 6.5%, 95% Confidence interval: -0.7% to 13.7%, two-sided p-value =0.08

- 45 deaths occurred in the treatment arm versus 35 deaths in the placebo arm at day 28.

Discussion

- How would you address the challenges of designing such a prevention trial including a large sample size, identification of at risk subjects, challenges with diagnosis of pneumonia, and confounding of safety assessments by underlying comorbidities?
- What other study designs and indications would you suggest for this or a similar product?