Challenges of HABP/VABP Trials

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Disclosures

- Employee of Cerexa, a wholly owned subsidiary of Forest Laboratories
- This presentation does not reflect an official position of Forest Laboratories

Risk of Seeking HABP/VABP Indication

Look at Recent History (2 from last 7):

- **Levaquin ~ approval**
  - **Based on open label study**
- **Linezolid ~ approval**
  - **Double-blind, 20% NI margin**
- **Meropenem ~ non-approval**
  - **Insufficient sample size (1996 NDA) & open-label non-comparative data (2004 sNDA)**
- **Televancin ~ non-approval**
  - **Regulatory change in endpoint after study**
- **Tigecycline & Ceftobiprole ~ each received non-approval**
  - **Concern re: efficacy in VAP cohort**
- **Doripenem ~ non-approval**
  - **Concern re: concomitant antibiotics**

Feasibility of Completing 1 Study

- Linezolid (circa 2000): ~400 patients in ~10 months from ~90 sites (~0.4 p/s/m)
- Telavancin (circa 2005): ~1500 patients in ~30 months from ~450 sites (~0.1 p/s/m)
- Studies harder now due to consent issues, VAP preventative measures more ubiquitous, new CDC definitions potentially decreasing reporting of VAP
- Are there enough qualified sites and what if multiple Sponsors pursuing HABP/VABP concurrently?
- If enriching for resistant pathogens, will result in ↓ enrollment rates

Global Regulatory Differences

- Increasingly more difficult to satisfy both FDA and EMA with one protocol
  - Risk: development of indication for only one regulatory body
- EMA guidance relatively clear
  - Primary Endpoint: Clinical Response at TOC
  - NI margin: 12.5%
  - Primary Populations: ITT and CE
  - Allow both HAP and VAP in one study
  - Allow limited (≤24 hours) prior antibiotics

Non-statistical Issues
Concomitant Therapy

Standard of care dictates empiric coverage:

- **MRSA**
- ***P. aeruginosa* (often double coverage)**
- ***Acinetobacter* in some geographies**

Therefore:

If new agent predominately G- coverage:

- **May need additional *P. aeruginosa* coverage**
- **Will need G+ coverage**

If new agent predominately G+ coverage:

- **Will need double coverage for *P. aeruginosa***
- **G- coverage likely to have overlapping G+ coverage**
  - **Result: monotherapy study drug against MRSA only**

Non-statistical Issues
Comparator Agent

- Not many agents approved for NP in US
- Difficult to blind with some agents (eg, tid vs qid dosing)
- Not always approved in countries needed for study
- Fluid restrictions affecting placebo dosing
- Fluctuating renal/hepatic dysfunction affecting dosing

Non-statistical Issues
Informed Consent

- Informed Consent
  - Patients are often unable to provide IC
  - Patients/families less likely to participate in “research” due to life-threatening nature of illness
  - Time required for IC may be prohibitive
  - IC Forms are too complex and long

Non-statistical Issues
Safety Reporting

- Complex patients with ↑↑↑ SAEs
  - Increased effort to collect/monitor safety data
  - Increased cost

Personal Thoughts on Endpoint

- **Clinical Response at TOC**
  - **FDA cannot find historical data to justify margin**
  - **Antibiotics clearly shown to affect mortality in pneumonia (therefore not similar to URTI)**
  - **3 drugs failed non-inferiority (daptomycin for CAP, and tigecycline and ceftobiprole for HAP)**
    - **Scientific rationale for "failures": either inhibition or dose issues**
  - **Appears to have assay sensitivity for drugs effective in other indications**

Note: All these studies allowed prior antibiotics and still a treatment difference was detected

Personal Thoughts on Endpoint (cont.)

- **Mortality at Day 28**
  - **Ability to detect difference against "enhanced-placebo" (delayed effective therapy)**
  - **Telavancin versus vancomycin**
    - **2 identically designed studies**
    - **Mortality treatment difference in opposite direction for the two trials**
    - **Therefore, lack of assay sensitivity for similarly effective drugs**

Conclusions

- Feasibility of HABP/VABP trials are multifactorial
  - We will be discussing these factors over the next two days
- Must think globally
- As presented by Brad Spelberg, anti-infectives are unique amongst drug therapies, so NI justification for anti-infectives should reflect this.
  - Maybe historical endpoints like clinical response at TOC are not “broken” and do not need to be “fixed”