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”