Development of Drugs for HAP-VAP

Robert Fromtling, MD
Hospital-Acquired & Ventilator-Associated Pneumonia (HAP-VAP)

• The EMA 2015 roadmap recognizes the need for new antibiotics
  – New drugs for HAP-VAP are urgently needed
  – HAP-VAP is a key testing ground for new Gram-negative agents
• Critical need for updated and clear guidance that encourages:
  – Informative clinical trial designs
  – Feasible clinical trial designs that encourage industry investment
  – Endpoints that are relevant to patients and physicians and that clearly assess the effectiveness of a new antibiotic
  – Need for uniform criteria for diagnosis of pneumonia among regulatory guidances and clinical treatment guidelines
Key Issues for Today

• Endpoint
  – Is All-Cause Mortality the correct endpoint?
    What is the appropriate time to assess the endpoint?
• Margin: Needs to be clinically meaningful and realistic
• mMITT (microbiologically proven) vs. ITT (all patients)
  – What level of microbiologic proof is needed?
• Can HAP and VAP be in the same trial with stratification vs. separate studies?
• Can antibiotics be used prior to trial entry?
Realistic & Informative Trial Design

- Acceptable trials must assess efficacy and safety in a fully representative patient population
  - Active-control, non-inferiority designs are required
  - Enroll patients only with strong HAP-VAP syndrome
  - In such patients, increased mortality seen with inadequate therapy e.g., there is a low spontaneous response rate
- Measure response before underlying disease influences outcome: early (7-14 d) likely better than late (28d)
- Margin & inclusions should be scientifically justifiable and lead to achievable trial size
- Limit prior antibiotics but do not exclude entirely
- Patients from all relevant extended health care settings (hospitals, nursing homes, ICU) should be permissible
What is the Correct Endpoint?

• Issue: All-cause mortality (ACM) has many limitations
  – As antibiotics have a clear effect on 28-day ACM, a recent position paper endorsed by 4 societies (IDSA, ATS, ACCP, & SCCM) suggests ACM be used the primary endpoint for HAP-VAP
  – But, attributable mortality would be preferred as the linkage of ACM is reduced by supportive care and underlying disease
  – Further, ACM “is not consistent with clinical practice.”
  – Finally, fever, oxygenation, etc. are routinely assessed. “Failure to consider (these) decreases clinical relevance and creates a risk that results of registration studies will not extrapolate well to post-approval use”

• Suggestion: ACM could be used, but clinical response based on fever, oxygenation, and survival is also plausible
  – Combes (Crit Care Med 2007; 35:146-54) showed changes in PaO$_2$/FiO$_2$ were linked to mortality

Statistical Analysis - Margin

• Issue: What is an appropriate margin for HAP/VAP?
• Concerns:
  – Non-inferiority margin up to 15% is:
    • Reasonable vs. strong historical data with effect of ~30%
    • Consistent with prior clinical studies and guidances
    • Provides some flexibility in study design
    • Reasonable if paired (2 confirmatory) studies are conducted
• Suggestion: Historical data estimates ~30% effect, so margins of up to 15% are supportable. Such margins are clinically reasonable and will greatly improve the success of enrolling studies and moderate the size of clinical studies.
mMITT vs. ITT (1 of 2)

• Issue: What level of bacteriologic confirmation is needed?
• Merits of ITT (Clinical diagnosis) population
  – Antibiotics give mortality benefit in ITT populations\(^1\)
  – ITT population is more representative of the future use of the drug
  – Uses all patients: Pathogen shown in only 30-40% of HAP-VAP cases\(^2\)
  – If mMITT is primary analysis, need 2,200 patients for 10% margin\(^3\)
    • 1000 for 15%
  – Avoids uncertainties of cultures (e.g., defining proper CFU cutoff)
• Merits of mMITT (microbiological proof) population
  – Seems logical to want to have an organism for a clinical trial
  – Is required for a narrow-spectrum agent
  – May reduce enrollment with syndromes mimicking pneumonia (confirm true HAP-VAP syndrome)

\(^1\)Sorbo, Drug Info J 2010; 44:165-176; \(^2\)Telavancin vs. vancomycin for HAP: ATTAIN*: 31% of randomized patients were in mMITT; \(^3\)Presumes 30% mMITT rate, 80% response rate.
mMITT vs. ITT (2 of 2)

- EFPIA suggests
  - Primary analysis would be of ITT population
  - This would be followed by a subset analysis for microbiologically proven cases
  - Minimum numbers (or percentages) of microbiologically proven cases could be agreed upon

- If mMITT required, must accept all types of microbiological proof
  - We should consider & employ all diagnostic tools possible, both cultures (blood, sputum, BAL) and non-culture-based methodologies
HAP-VAP: Separate Studies?

• Issue: Should HAP and VAP be studied separately or can they be studied together with proper sub-analysis?

• Concerns:
  – The syndromes are similar; VAP patients tend to have more severe infections than HAP patients (higher incidence of MDR organisms)
  – Prior studies allowed both (with stratification) → ATTAIN* had 70% HAP & 30% VAP
  – Feasibility issue for separate study of VAP
    • VAP represents about 32% of HAP-VAP patients - it will be difficult to impossible to enroll a VAP-only study with proper patient numbers
    – There is a concern of creating orphan “body-site” diseases

• Suggestion: Permit either separate studies or combined study with stratification (review design strategy via Scientific Advice)

*Telavancin vs. vancomycin for HAP
Prior Antibiotic Therapy

• Issue: Should prior antibiotic therapy be allowed?
• Concerns:
  – Prior antibiotics are common in this setting and lead to higher MIC values and more resistant pathogens
  – Very restrictive approaches (e.g., prior 30 days) will make enrollment very difficult
  – By excluding prior antibiotics, one narrows the generalisability of the enrolled population & the results
  – ATTAIN permitted prior antibiotic therapy: ~55% received prior antibiotics, including 30% failing prior antibiotics
• Suggestion:
  – Allow antibiotics within the 48 hours prior to enrollment
  – Stratification based on receipt of prior antibiotic therapy could be used to maintain balance across groups
Conclusion

• Critical need for updated and clear guidance that encourages:
  – Informative clinical trial designs
  – Feasible clinical trial designs that encourage industry investment
  – Endpoints that are relevant to patients and physicians and that clearly assess the effectiveness of a new antibiotic
  – Need for uniform criteria for diagnosis of pneumonia among regulatory guidances and clinical treatment guidelines

• EFPIA is concerned that overly restrictive guidance will make this area so unmanageable that no work will be done
  – Case in point: Developing a narrow-spectrum anti-pseudomonal agent via a fully powered mMITT-based analysis may not be possible