


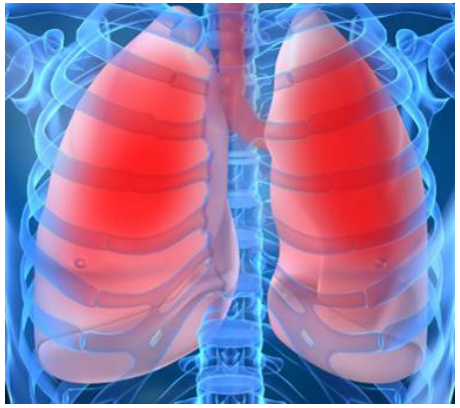

FIGHTBACK

EMA Workshop on update of TB Guideline
25 November, 2016
London, England

Topic 2: Efficacy endpoints in clinical trials: Industry Perspective


Otsuka

efpia

TB innovation for tomorrow.

Efficacy Endpoints and Efficacy Assessment

- Microbiologic
  - Early Endpoints
    - Early Bactericidal Activity
    - Sputum Culture Conversion (Initial and Final)
    - Time to Positivity
  - Late Endpoints
    - Primary Treatment Failure
    - Sustained Conversion
    - Relapse
- Non-microbiologic
  - Death
  - Resolution of Signs and Symptoms including imaging
- Host Factors
- Efficacy Assessment: Selection of the Comparator

Early Bactericidal Activity (EBA)

- Model developed by BMRC; Jindani et al. Am Rev Respir Dis. 1980, 121:939-949
- Design
  - Patient population = newly diagnosed, previously untreated, AFB smear positive pulmonary TB patients
  - Treat with single drug or drug combination for 14 days compared to an active control (HRZE)
  - Overnight, pooled sputum collection and culture
    - Quantitative culture on solid media
    - Assessment of time to detection in automated liquid culture system
- Highly predictive of bactericidal activity for current HRZE regimen, assumed to be predictive for new drugs and regimens

BMRC = British Medical Research Council; H = isoniazid; R = rifampicin; Z = pyrazinamide;E = ethambutol

Sputum Negativity and Sputum Culture Conversion (SCC)

- Proportion sputum negative reported in BMRC trials and used by Wallis et al. to predict relapse with various therapy
- Requires at least 2 sequential negative sputum cultures (28 days apart)
  - Initial (phase 2B) and final (phase 3) sputum SCC
  - Correlates well long-term outcomes for populations

Association of mortality and successful treatment with SCC at 2 months in MDR-TB patients*		
Achieve 2 Month SCC	Treatment Success at 24 Months	Mortality at 4 years
Yes	930/1090 85.32%	42/1090 3.85%
No	1068/1852 57.67%	309/1852 16.68%

*Unpublished data from investigators of the Collaborative Group for the Meta-Analysis of Individual Patient Data in MDR-TB

Wallis, Peppard and Hermann. 2015 PLoS ONE 10(4):e0125403.

Time to Positivity (TTP)

- TTP most often measured in automated liquid media culture systems
- TTP provides a measure of rate of bacterial clearance and regimen activity over time that might not be captured in the proportion SCC
- TTP can be affected by drug carry-over in sputum
- TTP can be affected by differences in bacterial populations

Late Microbiologic Endpoints

- Primary Treatment Failure
  - Failure to achieve negative sputum culture by a given time point may indicate the failure of a regimen
    - A 4-month regimen should result in ≥99% negative cultures by the end of 2-months treatment (Wallis, Peppard and Hermann. 2015 PLoS ONE 10(4): e0125403)
- Sustained Conversion/Reactivation/Reinfection
  - Isolated positive cultures may not be an indication of reactivation of disease
    - Five-year follow-up shows low risk of reactivation (Hong Kong Chest Service/BMRC Am Rev Respir Dis 1987; 136:1339 and Am Rev Respir Dis 1988; 137:1147)
    - Genotypic analysis may help differentiate reactivation from reinfection or contamination
  - Repeat positive cultures with the same genotype as the baseline isolate are likely indicative of reactivation of disease

Non-microbiologic Endpoints

- Mortality
  - Excluding deaths clearly not linked to study drug included in the draft guideline
  - Analyzing all deaths at least as a sensitivity analysis, including mortality assessment of patients withdrawn from the study
- Resolution of Signs and Symptoms
  - RCT of streptomycin assessed radiographs, general condition, temperature, body weight, sedimentation rate and bacillary load
  - Measuring changes in cough frequency, BMI, inflammatory markers and advanced assessment of chest radiographs
- Imaging
  - Assessment in changes in serial chest radiographs (exploratory end point in Otsuka Phase III trial)
  - Proposed evaluation of PET/CT to measure changes in inflammation and structural damage of the lung
- Host factors and Biomarkers
  - Multiple cytokines proposed as markers of disease progression and cure
  - Measurement of LAM in sputum as a biomarker of bacterial load

Efficacy Assessment: Selection of the Comparator

- Gold standard comparator is always the concurrently enrolled, randomized control
- Non-Concurrent (Historical) Controls
  - Suggested in some discussions around studies of AMR (anti-microbial resistance), particularly infections with high mortality
  - MDR/XDR treatment paradigms and outcomes dramatically changing

MDR-TB 5 year cohort	1996-2000 (N=86)	2001-2005 (N=125)	2006-2010 (N=123)
% Success	53.5%	68.8%	83.7%
% Mortality	10.5%	8.0%	4.1%

Kwak et al. Int J Tuberc and Lung Dis. 2015, 19(5):525-530

"This improvement could be explained by the broader use of FQ's and the introduction of linezolid"

  - Non-concurrent control must be as similar as possible to a cohort of patients treated with a regimen that would be approved as a control by an IRB today

Summary

- Microbiologic endpoints are likely to remain the gold standard for quite awhile
  - SCC or proportion negative at early time points
  - Sustained conversion for 6 – 12 months as the only marker of bacterial sterilization
- Non-microbiologic endpoints
  - None are validated as an endpoint for cure but may be useful as early markers of efficacy
- Host factors and Biomarkers
  - None are validated as endpoints for cure
  - Likely to first be used as drug development tools
    - ❖ Procedures for qualification of new Drug Development Methods are available

Thank you!