Innovative trial designs to evaluate new treatment combinations for TB

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Outline

• Why do we need novel trial designs?
  • Slow pathway to combination development
  • Unclear relationship between phase II and phase III endpoints.

• What is possible?
  • Ongoing or planned novel trials design for new TB treatment

• How can we do it better?
  • Possibilities for future studies
  • Research gaps
Why do we need novel trial designs?
Case studies of bedaquiline and delamanid

Bedaquiline – accelerated approval from US FDA Dec 2012

• “[Is accelerated approval justified] ...based only on a measure of sputum changes in the face of contradictory evidence from clinical end points such as treatment failure and death?”
  • Avorn J. Approval of a tuberculosis drug based on a paradoxical surrogate measure. JAMA

• “As uncertainties remain about the relative benefits and harms when using bedaquiline, caution is advised when other options ... still exist.”
  • The use of bedaquiline in the treatment of multidrug-resistant tuberculosis: Interim policy guidance, WHO, 2013

• Phase III results expected 2020
Case studies of bedaquiline and delamanid

Delamanid
- European Medicines Agency (EMA) refused the marketing authorisation for delamanid for MDR-TB in July 2013.

- “...the data from two months’ treatment could not be used to predict the effectiveness of Delamanid when given for six months.”
  - “Questions and answers on the refusal of the marketing authorisation for delamanid”, 26th July 2013, EMA.

- Submission for approval has been filed with Japanese regulators.

- Phase III results expected 2015/2016
How do we evaluate drugs and combinations for efficacy and safety?

Pre-clinical studies:
- Animal models
- In vitro studies

Phase II studies:
- Dose-ranging PK
- 14-day EBA
- Whole blood assay

Early indication of efficacy of individual drugs and limited data on combinations

Confirmatory proof of combination efficacy

Phase III Randomised Controlled Trial

Gold standard for confirmation of efficacy

Big Gap!
14-day bactericidal activity (EBA) does not predict sterilizing activity

Figure: Published trials of quantitative sputum microbiology in patients with pulmonary tuberculosis of 7–28 days’ duration
Left: Across-trial comparisons of similar treatments, showing similar results. Right: Within-trial comparisons of distinct treatments, showing similar results during first 14 days. H=isoniazid; R=rifampicin, E=ethambutol; S=streptomycin, Z=pyrazinamide; T=thiacetazone. CFU=colony-forming units.

Cultures at 2 or 3 months are not reliable surrogate endpoints


MRC Trials in East Africa
The two month culture failed to predict long-term outcome in RIFAQUIN

RIFAQUIN Treatment Arms:

- **Control Regimen** *(2EHRZ/4HR)*
  - 2 months of daily ethambutol, isoniazid, rifampicin, and pyrazinamide followed by 4 months of daily isoniazid and rifampicin.

- **4-month Regimen** *(2EMRZ/2P2M2)*
  - Isoniazid replaced by moxifloxacin in the 2-month intensive phase and two months of twice-weekly moxifloxacin and 900mg rifapentine.

- **6-month Regimen** *(2EMRZ/4P1M1)*
  - Isoniazid replaced by moxifloxacin in the intensive phase and four months of once-weekly moxifloxacin and 1200mg rifapentine.

<table>
<thead>
<tr>
<th>Culture result</th>
<th>2-month Intensive Phase</th>
<th>( \chi^2 ) test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RZE + H</td>
<td>RZE + M</td>
</tr>
<tr>
<td><strong>Negative</strong></td>
<td>187 (85%)</td>
<td>394 (90%)</td>
</tr>
<tr>
<td><strong>Positive</strong></td>
<td>32 (15%)</td>
<td>42 (10%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>219</td>
<td>436</td>
</tr>
</tbody>
</table>

Preliminary results, the RIFAQUIN Trial Team [manuscript in preparation]
Bridging the gap

• Many new and re-purposed compounds are in clinical development

• How can combination regimens be identified quickly for evaluation in Phase III that are
  • safe,
  • well tolerated,
  • most likely to prevent relapse?

• Adaptive trial designs
  • Formally integrate decision-making into trial design
  • Quantify and manage risks
What is possible?
Planned or ongoing trials with novel designs

Adaptive designs
1. Phase II trial of daily rifapentine
2. MARVEL trial in MDR-TB
3. PanACEA MAMS-TB

Incorporating special patient populations
4. SHINE paediatric TB study
5. NC-002

Design concepts
6. Bayesian reanalysis of TBTC Study 28
7. Duration randomisation
1. Phase II trial of daily rifapentine: Simon’s Optimal 2-stage design

- Optimal 2-stage design proposed in 1989 by Simon.

Principal investigators:
- Susan Dorman, Rodney Dawson, Richard Chaisson.

- Study is complete, analysis ongoing with results expected Q4 2013.

### Stage 1:
Randomise 45 patients

- 8 weeks treatment (+HZE)
  - Rifapentine 450mg
  - Rifapentine 600mg
  - Rifampicin 600mg

Screen for eligibility

Enrolment pause

Discard any rifapentine regimen where <6 of 11 evaluable patients have 8-week culture conversion.

### Stage 2:
Randomise 36 patients per arm

- 8 weeks treatment (+HZE)
  - Rifapentine 450mg
  - Rifapentine 600mg
  - Rifampicin 600mg

Screen for eligibility

2. MARVEL trial in MDR-TB
Interim efficacy analysis to drop arms for lack of benefit

- Planned interim analysis for efficacy after 16 participants on each arm have 8-week culture results.
- Drop arms with **fewer than 4 of 16 participants culture negative at week 8**.

- Study protocol in development with ACTG
- Principal investigator: C. Robert Horsburgh Jr.
3. PanACEA MAMS-TB
Interim efficacy analyses to drop arms for lack of benefit

- Pan African Consortium for Evaluation of Anti-tuberculosis Antibiotics (PanACEA)
  - 5 European and 11 African Partners
  - Funded by EDCTP

- Three drug development programmes:
  - Moxifloxacin (REMoxBTB)
  - High-dose rifampicin (HIRIF EBA)
  - SQ109 (SQ109 EBA)

See [www.panacea-tb.net](http://www.panacea-tb.net) for more details
3. PanACEA MAMS-TB
Interim efficacy analyses to drop arms for lack of benefit

- Primary endpoint of time to stable culture conversion on liquid media

- Planned **interim analysis** after 28 control patients culture converted to negative
  - Each experimental arm will be **compared with the control in pair-wise comparisons**
  - Decisions based on pre-specified stopping rules
Potential final sample sizes
Expected final sample sizes
4. SHINE: Shorter treatment in childhood TB

Uncertainty in appropriate weight bands and dosing of rifampicin in children.

Nested PK studies early in the trial to adapt dosing or weight bands as necessary.

Protocol in development

Funding from MRC/DFID/Wellcome trust

Principal investigator: Di Gibb, MRC CTU

Screen for eligibility

Children 0 to 12 with diagnosis of minimal TB

Randomise a total of 1200 participants

2HRZ(E)/2HR

2HRZ(E)/4HR

First 34 enrolled in PK sub-study

First 34 enrolled in PK sub-study

Adjust dosing or weight bands as necessary
5. TB Alliance NC-002 phase II
Concurrent enrolment of MDR-TB cohort

- 8-week SSCC study, sample size = 230
- DS-TB patients randomised among 3 regimens
- Cohort of MDR-TB patients concurrently enrolled on 200mg PaMZ regimen.
- Results expected Q4 2013
6. TBTC Study 28
Retrospective Bayesian reanalysis

- TBTC Study 28 showed substitution of moxifloxacin for isoniazid resulted in **no difference in week-8 culture negativity**.

- 433 participants were randomised over 13 months.
  - 328 (74%) eligible for primary analysis

- **Could this study have been stopped earlier using Bayesian predictive probabilities?**

- Work by David Holland and Alaattin Erkanli from Duke University
6. TBTC Study 28
Retrospective Bayesian reanalysis
6. TBTC Study 28
Retrospective Bayesian reanalysis

- Allowing for:
  - 8 weeks patient follow-up
  - 6 weeks culture growth (liquid media)
  - 4 weeks for data entry, cleaning, analysis and time for decision to terminate study
  - 105 (24%) excluded from primary analysis (protocol correct group)
  - Total sample size of 433 recruited over 13 months from February 2006 to March 2007.
6. TBTC Study 28
Retrospective Bayesian reanalysis
7. Randomisation to multiple durations of the same regimen

Figure 2 Logistic regression estimates of odds ratios for a cure on Regimen A compared to standard regimen by duration of treatment with Regimen A in a single simulated trial using the proposed trial design. Odds ratio estimates are shown by the solid circles connected with the solid line, while the upper and lower 95% CI bounds for these estimates are shown with solid circles connected by dashed lines. The non-inferiority boundary of 0.63 is shown by the horizontal line at that level on the vertical axis. The vertical axis is presented on the log scale. CI, confidence interval.

How can we do better?
Tools to improve how we do clinical trials

1. Bayesian Predictive inference
2. Seamless phase II/III trials
3. Better real-time biomarkers that reliably capture sterilizing activity
4. Rapid data entry and data management
5. More efficient trial designs
1. Bayesian Predictive Inference

• Given all that we know about a combination regimen (animal, in vitro, mechanism of action, 14-day EBA, etc.)

AND

• the results of 8-12 week phase II trials:

  • What is the probability that a shorter regimen will be non-inferior in a phase III trial?

• ‘Assurance’ – beyond power
Predicting the relapse rate given the proportion culture positive at month 2


80% predictive intervals
2. Seamless phase II/III trial design

- Phases II and III are interwoven into a single trial.

- Regimen(s) are selected for Phase III stage on the basis of an intermediate endpoint.

- All patients are followed up for long-term endpoints.

- Single trial protocol with pre-specified decision rules for regimen selection.
3. Better real-time biomarkers that reliably capture sterilizing activity

- Molecular bacterial load (MBL) assay

- GeneXpert Cycle Threshold
Early relapse as an early indicator of a failing regimen in a phase III trial?

- **RIFAQUIN**
  Preliminary results, the RIFAQUIN Trial Team [manuscript in preparation]

- **4th MRC E African Study (4-month regimens)**
4. Rapid data entry and data management

- Accurate, current data is essential for decision-making in adaptive trial designs.

- Tablets for eSource (PanACEA MAMS-TB)

- Mobile phone data collection (XTEND study)

- Near real-time data centrally

- Both allow for local data capture if signal is intermittent

- Focus more on central monitoring of data
5. More efficient trial designs

- Adaptive randomisation – “*Play the winner*”
  - Frequent interim analyses
  - Allocation ratio adjusted in favour of best performing regimens
- **Multi-stage seamless phase II/III**
  - Stage 1: 14-day intensive safety assessment
  - Stage 2: 8-week intermediate efficacy assessment
  - Stage 3: 18-month long-term efficacy assessment
- **Stratified medicine**
  - Biomarker-driven randomisation for individualised regimens
- **Other Bayesian designs**
- Many others...
Conclusions
Conclusions

- The current clinical development pathway for new combinations for the treatment of TB is slow and faltering.

- Adaptive and other novel trial designs have been used with much success in other disease areas.

- These designs should be used in TB trials to speed regimen development.
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Further reading