Issues in TB Drug Development for Sensitive Disease

Clinical Development

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Aim of Development of New drugs for TB

• *Programmatic point of view:*
  – To shorten treatment to ≤4 months so as to radically improve TB control (improve adherence, simplify treatment delivery and decrease drug resistance)

• *Regulatory point of view:*
  – to provide persuasive evidence that clinical outcomes of new therapy are at least comparable to those of standard therapy
  – both in general population and in specific sub-groups (HIV infected persons)
Microbiology aspects

• Different populations of *M. tuberculosis* organisms in TB disease
  – drugs have varying levels of activity against these different populations
  – killing of slowly-multiplying organisms (acidic environment) and sporadically-multiplying organisms

• Negative sputum cultures after 2 months of treatment generally conceived as indicative of sterilizing activity

• Shorten TB therapy: accelerate killing of *M. tuberculosis*, especially during the 2 first months of therapy
Main Issues in Clinical Development

• Very long timeline of clinical trials after pre-clinical stages:
  – Phase I studies: drug toxicity; PK
  – Phase II studies: prove that drugs are active in human disease and capable of shortening treatment:
    • bactericidal activity of new drugs
    • combinations with other drugs
    • drug-drug interactions
Main Issues in Clinical Development

- Phase III trials in TB: large and lengthy
  - standard therapy is very effective (<5% relapse), so large sample sizes are needed (>1000-2000)
  - non-inferiority design
  - choice of endpoint: relapse usually requires observation 12-24 mths after end of treatment;
  - no efficient and accepted surrogate markers of treatment efficacy
  - costly (often tens of millions of dollars)
  - need of appropriate clinical trial capacity in trial sites
  - access to large numbers of patients
Long timeline of clinical trials

- At least 6 years for the clinical development of a drug (conservative estimate)
- If considering a totally new 3-4 drugs regimen, >2 decades needed!
- So, need to find the optimal combination early!

→ **Phase II: key step** in deciding which of the many new drugs/regimen that have activity in animal models and/or early clinical development phases are sufficiently promising to warrant the time and expenses of a Phase III trial
I. Assessment of bactericidal effects - Phase II studies

- Bactericidal activity: *has the new drug/ regimen proposed a proven bactericidal impact?*
  → *Phases IIA studies: EBA studies*

- “Sterilising power”: *would the speed of killing bacilli be accelerated to allow shortened regimens?*
  → *Phase IIB studies:*
    - 2 months culture conversion
    - time to sputum conversion
    - SSCC studies
1. EBA studies

• Prove that a drug is bactericidal against TB bacilli in cavities by measuring the fall in bacillary content in sputum during the first days of treatment;

  – Small groups of patients given monotherapy with a selected drug for a few days

  – Sputum collected overnight during the period

  – Counts of viable bacilli in selective culture media

  – EBA of a drug usually expressed as the fall in log colony count/ml sputum/ day
EBA studies

- **2 phases of killing** (Jindani et al, AJRCCM 2003; 167:1348)
  - 0 - 2 days: rapid exponential fall: killing of the multiplying bacilli
    - effective in showing differences between drugs and between different doses of the same drug
    - Reflects penetration of the drug into cavities
  - 2 - 14 days (~ 1 month): slower fall
    - presumably due to killing of persisters (responsible for prolonged treatment),
    - less efficient in showing differences between drugs and doses (and therefore the penetration into cavities)
    - estimation of sterilizing activity
Counts of colony forming units (cfu) on selective medium from patients with pulmonary TB during the first 4 weeks of therapy with SM/INH/RMP/PZA (Nairobi 1 - Jindani et al, AJRCCM 2003; 167:1348) or with regimens with INH (Nairobi 2 - Brindle et al, BMC Pulmonary Med 2001;1:2)
Possible designs of EBA studies

- **Simple EBA (2-6 days):**
  - single dose new drug
  - shows bactericidal activity of a new drug on bacilli in cavities
  - ratio of the kill during the first 2 days to the kill from 2-5 days may hint at the sterilizing activity of the drug

- **Dose-ranging EBA (2 days only):**
  - allows demonstration of the minimal effective dose (MED) and estimation of therapeutic margin
Titration of dose size against EBA 0-2 for INH, RMP and STM (Sirgel et al, AJRCCM 2005;172:128) - MED size: INH: 15 mg; RMP: 150 mg; SM: 0.5 g (EBA = 0)
Possible designs of EBA studies

• *Extended EBA (14 days)*:
  – monotherapy during 14 days,
  – possibility to compare with standard 4-drug therapy,
  – useful for drugs with very slow bactericidal activity,
  – ethical concern (possibility of giving inactive treatment for too long a period → need to give full treatment immediately thereafter).
TMC207 C202 EBA Trial -2007

Changes in cfu counts over time* with 95% CL

*SOC administered day 8

Courtesy of Tibotec, Inc.
A rational choice of EBA study? (D. Mitchison)

New drug being investigated for the first time:

- initial EBA study over 14 days with a single high dose
  - establish whether the drug is active at this high dose,
  - whether there is a delay in the onset of bactericidal activity,
  - provide some information on whether it might be a sterilising drug

- if no delay in the onset of bactericidal activity, then conduct a second EBA study in which the drug is tried at lower doses
  - treatment for 2 days would be sufficient
  - can help determining MED + therapeutic margin
2. Sterilising activity

**Aim:**
- proves that a new drug can accelerate killing
- investigates the best combination for effective treatment
- May be guided by studies in animal models (e.g. experimental murine TB)

**Various markers:**
- 2 months sputum conversion
- Time to sputum conversion
- SSCC studies
In mice, substitution of moxifloxacin for isoniazid results in increased antimicrobial activity.
2.1 Two-months sputum conversion

- BMRC trials: proportion of patients whose sputum becomes negative on culture at 8 weeks correlates with proportion of patients who relapse after end of treatment (Mitchison D, 1996)

- It is suggested that a regimen with higher rates of 2-month sputum conversion will allow substantial shortening of treatment (as compared to standard regimen)

*But*

- Single dichotomous outcome at a fixed time point
- Requires large sample sizes (100 – 200 pts/arm)
- Differences in culture conversion between liquid (broth) cultures and solid (agar) culture media (Oflotub, TBTC Study 28)
- Needs further exploration: may provide clues to biological variation among populations of patients and bacilli
Evaluation of the activity and tolerability of moxifloxacin during the first two months of treatment for pulmonary tuberculosis: TBTC Study 27

Two-month Sputum Culture Conversion By Study Arm and Factorial Design

<table>
<thead>
<tr>
<th>Treatment</th>
<th>5 days/wk</th>
<th>3 days/wk</th>
<th>Combined*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moxifloxacin</td>
<td>48/68 (71%)</td>
<td>51/71 (72%)</td>
<td>99/139 (71%)</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>52/68 (76%)</td>
<td>46/70 (66%)</td>
<td>98/138 (71%)</td>
</tr>
<tr>
<td>Combined</td>
<td>100/136 (74%)</td>
<td>97/141 (69%)</td>
<td></td>
</tr>
</tbody>
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Overall, p = 0.52.

*Comparing drug treatment arms, p = 0.97
Comparing treatment frequency arms, p = 0.39.

TBTC 27 - Sputum culture conversion rates with moxifloxacin higher at 4 and 6 weeks but not at 8 weeks

Burman WJ. AJRCCM 2006;174:331-8
OFLOTUB Phase II SSACC study

Screening
Newly diagnosed smear +ve
412

Willing to collaborate
226

Excluded
11

HRZE
Control
54

HRZO
Oflo
55

HRZG
Gati
54

HRZM
Moxi
54

RH
continuation

8-weeks

4 months

Negative sputum cultures at 8 weeks

7H11 $\chi^2_{[3]} = 11.8, \ p = 0.008$: MGIT $\chi^2_{[3]} = 1.7, \ p = 0.6$
2.2. Time to sputum conversion

• Survival techniques can more accurately reflect the effect of time on binary endpoints measured repeatedly (sputum sampled at weekly intervals over the 2 months)
• Time point after which all cultures become negative
• Continuous measure
• Speed of conversion seems a more sensitive indicator than the proportions negative at 8 weeks
OFLOTUB SSCC study

Hazard ratios

No covariate adjustment
p v. control
Gati 0.3
Moxi 0.009
Oflo 0.6

Covariate adjustment
p v. control
Gati 0.054
Moxi 0.017
Oflo 0.4

Log rank test
\( \chi^2 (3) = 10.69 \)
p = 0.0136
2.3 Serial Sputum Colony Counts (SSCC) studies

- Origin: extension of colony counting beyond 14 days (explored only once before in Brindle et al, BMC Pulm Med 2001)

- Parameters represent rate of decline of colony count

- OFLOTUB 2B: first study to extend this approach throughout the first 8 weeks

- Apply new modelling techniques for best estimation of fall in counts in unit time for each patient
  - taking into account errors involved in multiple counts on any one patient and
  - the variation between the patients themselves (Davies 2006)
Comparative bactericidal assessments

14 hour sputum collection

Sputum colony counts on selective 7H11 medium without decontamination at 10 time points during initial 8-week phase

- 0 2 7 14 21 28 35 42 49 56

- Standard 7H11 culture + indirect susceptibility tests
- Standard 7H11 culture
- Standard 7H11 culture + Liquid culture (MGIT)
Summary of SSCC results

Log$_{10}$CFU / ml sputum

Days on therapy

Limit of detection
Regression modelling of serial sputum colony counts

- Early fast phase lasting about 7 days, probably acting on multiplying bacilli
- Late slower phase continuing at least 8 weeks, probably measuring slow elimination of persistent bacilli
SSCC Study - Estimated treatment effects over initial 2 months combined therapy

No covariate adjustment

SSCC Study - Estimated treatment effects over initial 2 months combined therapy (adjusted on age, sex, HIV & extent of disease)

Characteristics of SSCC analysis (1)

- Regression modelling of SSCC data appears to be a suitable and efficient method for Phase II studies of novel combination regimens.
- Incorporation of *random effects*
  - reduces bias in parameters estimates,
  - allows individual variability in response
  - and accounts for within patient correlation to accurately reflect the variability of the estimates
- Continuous measurement
- It may have significant advantages as an endpoint over simple proportions and survival analysis
- Greater statistical efficiency
Characteristics of SSCC analysis (2)

- Able to distinguish between effects on early and late phase activity
- Comparison with established regimen
- Requests fewer patients
- Less costly
- Investigate relationship with ultimate relapse rate (Phase III trials)
II. Combined regimens

• Presently, testing substitution of individual drug one at a time
• Contribution of individual drugs?
• How to prove the efficacy of a single drug?
• Drug-drug interactions?
• Interaction with concomitant therapy (ARVs)?
III. Site capacity

- develop appropriate capacity to test all compounds presently in clinical development
- must meet GCP/GLP requirements
- high demands on potential sites
- findings from Phase II studies with variable culture media results in various populations may lead to the need of evaluating new compounds in diverse populations
IV. Ethical aspects

- Current therapy is highly efficacious (95% cure rate in clinical trials conditions)
- Few weeks of monotherapy may be enough to develop drug-resistance
- Considered as not ethical to test single drugs beyond 2 weeks
  → new drug evaluated for efficacy in the context of combined therapy
V. The challenge of “efficacy”

- Efficacious regimen in clinical trials → transfer in guidelines and policy
- Efficacy vs efficiency
- 8 months regimen less efficacious than the 6-months regimen but problem of RMP resistance
- Importance of Phase IV trials to
  - evaluate tolerability,
  - efficacy in large cohorts,
  - detect rare side effects,
  - unusual treatment outcomes,
  - key subgroups
- Programmatic aspect: OR studies investigating access to drugs, adherence to treatment, feasibility of new regimens, cost-effectiveness
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