

TBTC MDR-working group

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Types of studies – active TB

- Phase 1 – initial use in humans; dose-ranging
- Phase 2 – EBA, initial evaluation of efficacy and tolerability of multidrug therapy
- Phase 3 – treatment failure/relapse
- Phase 4 – evaluation of tolerability, efficacy in very large cohorts to detect rare side effects, unusual treatment outcomes, key subgroups

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PK studies

PD analysis

Possible endpoints for TB treatment trials

Endpoint	Comments
EBA	<ul style="list-style-type: none">• Sample size: 10-15 per arm• Dose-ranging, comparison of members of the same class• Poor correlation with sterilizing activity
2-month culture conversion	<ul style="list-style-type: none">• Sample size: 80-200 per arm• Correlates with risk of relapse (sterilizing activity)• Sufficient sample size for initial assessment of tolerability

Possible endpoints for TB treatment trials (continued)

Endpoint

Comments

- Quantitative sputum culture (SSCC)
 - Sample size: 35-50 per arm
 - Correlation with risk of relapse in 2 studies, requires further validation
 - Technically-demanding, dedicated lab
- Relapse
 - Sample size: 300-750 per arm
 - Definitive measure of treatment efficacy
 - Requires follow-up for 1-2 years after treatment completion

What kind of trials are needed to optimize MDR-TB treatment

- Phase 2
 - Early Bactericidal Activity (EBA)
 - Initial evaluation in multidrug therapy – pick dose, dosing interval from studies of drug-susceptible disease, if possible
- Phase 3 – try to define how to use drugs with promising activity in Phase 2
 - Treatment duration
 - Dosing frequency

MDR-TB clinical trials – the limitations

- Limited numbers of patients (in most settings)
- Substantial heterogeneity in clinically-relevant factors
 - Extent of drug resistance
 - Extent of prior drug exposure (whether associated with resistance or not)
 - Severity of pulmonary disease
 - HIV serostatus
- Very limited funding

Conclusion - a limited number of studies will be possible

Possible trial designs – Phase 2

- Randomize to
 - Optimized therapy (based on treatment experience and drug susceptibility testing) + placebo
 - Optimized therapy + new drug
 - or
 - Standard MDR regimen + placebo
 - Standard MDR regimen + new drug
- Possible endpoints
 - 2-month culture conversion
 - Change in quantitative sputum culture

Dealing with success in Phase 2

- Consider option to offer all patients access to the new drug if culture positive at 4 months
- Need to consider how long the new drug can be given to patients in either arm
- Once efficacy has been demonstrated, all patients should be offered the new drug
- A drug with demonstrated efficacy will become part of the standard of care, but additional studies will be necessary

Dealing with success in Phase 2

- Additional studies will be needed to understand the ramifications of the new standard of care and to detect delayed toxicity
 - Effect of the new regimen on duration of therapy: randomization to 2 different durations of therapy including the new drug
 - Observational cohort data on long-term tolerability / safety