17TH ANNUAL CONFERENCE OF THE BRITISH HIV ASSOCIATION (BHIVA)

British HIV Association BHIVA

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MRC Clinical Trials Unit

New Regimens for MDR-TB

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6th April 2011

MRC | Medical Research Council

MDR & XDR-TB

- MDR-TB: resistance to at least rifampicin and isoniazid
- Extensively drug resistant TB (XDR-TB): MDR-TB plus resistance to a flouroquinolone and at least one second line injectable agent

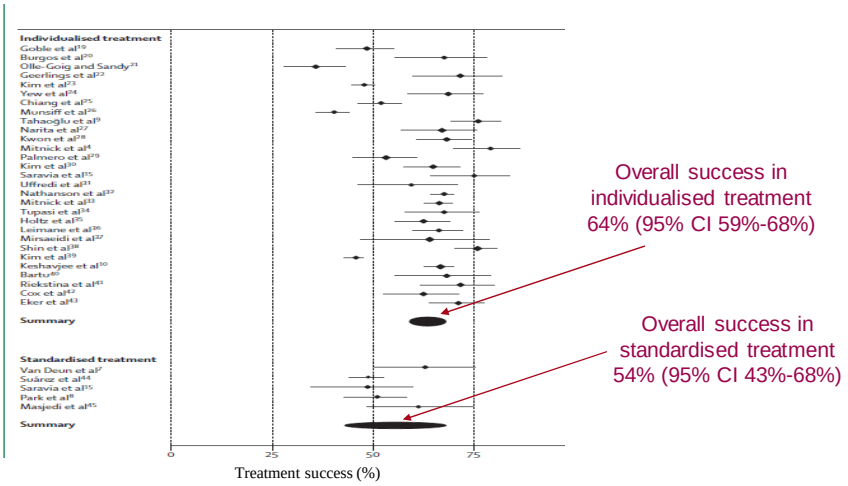
  XDR-TB has been reported from at least 57 countries

MDR-TB epidemic

- ~500,000 MDR-TB cases annually
- 5.4% of estimated 9.3 million cases world-wide
- Treatment with 6 or more 2nd line drugs for 18-24m
- Estimated 34% of MDR-TB cases in 2008 died
- **Overall cure rates ~ 60% (data on 71 countries)**

Meta-analysis: Orenstein E W et al. Lancet Infectious Diseases. 2009; 9: 153-61.

Orenstein meta-analysis



Magnitude of the drug resistant TB problem

	Any resistance	Isoniazid resistance	MDR-TB
New cases	17.0%	10.3%	2.9%
Previously treated cases	35.0%	27.7%	15.5%
All cases	**20.0%**	**13.3%**	**5.4%**

TMC207

- TMC207, is owned by Johnson & Johnson and is being developed at its research subsidiary Tibotec.
- Potently inhibits drug-sensitive and drug-resistant *M. tuberculosis* isolates and is bactericidal against dormant tubercle bacilli.
- In the murine model, TMC207 is as active as the combination of isoniazid, rifampicin and pyrazinamide
- Long half-life (permitting the possibility of once-weekly dosing), and acceptable adverse-event rates.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 4, 2009 VOL. 360 NO. 23

The Diarylquinoline TMC207 for Multidrug-Resistant Tuberculosis

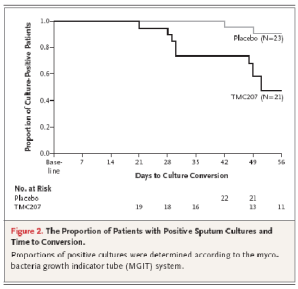


Figure 2. The Proportion of Patients with Positive Sputum Cultures and Time to Conversion.

Proportions of positive cultures were determined according to the myco-bacteria growth indicator tube (MGIT) system.

Conclusions

- Significantly faster culture conversion, **48% v 9%** culture negative at 8 weeks
- Good safety profile
- Potential for treating MDR and possibly fully sensitive disease.

TMC207 – report of Phase 2 trial

- The addition of TMC-207 to a 5-drug optimised background treatment regimen resulted in faster culture conversion by 24 weeks.
- Sputum conversion rate at 24 weeks of 79% on TMC207 regimen vs 58% on control, p=0.008.
- Shorter median time to 50% culture conversion, 12 v 18 weeks

TMC207 future plans

- Tibotec is in discussion with the regulators re:plans for accelerated approval and the design of a Phase 3 trial.
- Need to maintain a balance between making it available fast to those in greatest need and ensuring it is used judiciously.
- Repeatedly adding TMC207 to potentially failing second-line regimens would risk developing TMC207 resistance.
- Plans to include TMC207 in studies with OPC-67673 (Otsuka Pharmaceuticals) a nitroimidazole in phase 2b.

Can we do better? - the Bangladesh experience

- Series of cohorts studied
- 206 proven MDR-TB patients
- High dose gatifloxacin based regimen:
  - only 9+ months duration, rather than 18-24m
  - relapse-free cure / successful completion 87.9%
- Adverse events manageable
- Affordable: about 220 Euros drug costs
- **Not a randomised clinical trial**
  - **are the results too good to be true?**

Van Deun A et al. Short, highly effective and inexpensive standardised treatment of Multidrug-resistant Tuberculosis. Am. J. Respir. Crit. Care Med., May 2010.

STREAM

- The evaluation of a **S**tandardised **T**reatment **Re**gimen of **A**nti-tuberculosis drugs for patients with **M**ulti-drug resistant tuberculosis
- **STREAM** is the first Phase 3 evaluation of an MDR-TB regimen
- **Sponsor:** International Union Against TB and Lung Disease
- **Funder:** USAID
- **Trial Coordination**: MRC Clinical Trials Unit

STREAM: Study Regimen

Patients on the study regimen will receive:

Ethambutol, Pyrazinamide, Prothionamide and high dose Moxifloxacin daily for 9 months supplemented by Clofazimine, Kanamycin and high dose Isoniazid (H) for the first 4 months.

In the event of slow smear conversion the intensive phase can be extended to 6 months.

STREAM: design summary

- Consenting eligible patients will be randomised in a 2:1 ratio to receive either:
  - the study regimen, or
  - the local standardised WHO approved 18-24m regimen

  in a non-inferiority design
- Assumptions
  - 70% favourable response in control WHO regimen
  - 75% in study regimen
  - 10% margin of non-inferiority

    ~400 patients to be enrolled
- All patients will be followed up to 27 months post-randomisation.

STREAM: Primary outcome

Favourable:

- Culture negative at the end of follow-up (27 months) unless previously unfavourable

Unfavourable:

- Death at any time
- Failure to culture convert after 6 months
- Relapse
- Change of treatment or retreatment.
- Culture positive when last seen.

STREAM: which countries will be involved?

- Four countries, with satellite sites.
- Countries currently under consideration:
  - Ethiopia
  - India
  - South Africa (including HIV-coinfected participants)
  - Viet Nam
- Enrolment planned to commence in September 2011

Green Light Committee

- Standards for treatment differ widely between countries.
- Low income countries have the opportunity to provide high-quality treatment meeting international standards through the WHO Green Light Committee (GLC) Initiative at preferential prices.
- Since starting its work in 2000, the GLC has now approved treatment in over 70 countries
- However only 1% of MDR cases treated in 2008 ~ 2.5% in 2009; sites participating in **STREAM** will have been approved by GLC and receiving GLC drugs.

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