Sirturo: a new treatment against multidrug resistant tuberculosis
TB is an on-going problem

WHO estimated incidence of new TB cases 2009

Global Tuberculosis Control: WHO report 2010. Available at:
Tuberculosis Is the Most Common Infectious Disease

- Worldwide, 2 billion people are infected with TB (LTBI)
- 16 million+ patients have active TB
  - 9.27 million new cases in 2007
  - = 139 cases per 100,000 population
  - 2 million TB deaths per year
    - 1.32 million people not infected with HIV
    - 456,000 people who were infected with HIV
- 95% of TB cases and 98% of TB deaths in low- and middle-income countries
  - 22 high burden countries account for 80% of cases (India, China, Indonesia, Nigeria, South Africa)

  ➢ Globally, tuberculosis is the #1 cause of death in HIV+ patients

- MDR-TB cases = 500,000 in 2007 (289,000 new cases, with highest rates in India, China, Russia, South Africa, Bangladesh)
- 55 countries have reported cases of XDR-TB by the end of 2008
Treatment of MDR-TB: general principles

• Use at least 4 drugs certain to be active
  – Drugs to which resistance is known to be rare
  – DST results show susceptibility (with good laboratory reliability e.g. injectables, fluoroquinolones)
  – Drugs not commonly used in the area
  – Drugs with no prior history of failure in an individual patient
• Do not use drugs for which there is a possibility of cross-resistance
• Eliminate drugs that are not safe
• Include first-line agents, injectables and fluoroquinolones before other options
• If DST unavailable, a standard regimen is proposed by WHO

TMC207 pre-clinical data
In strains resistant to TMC207, mutations were identified in the gene coding for ATP synthase.

Provides energy (ATP) from a trans-membrane proton gradient.
A New Mechanism of Action

Cell Wall (peptidoglycan) Synthesis
β-lactam drugs
Vancomycin
Bacitracin

Nucleic Acid Synthesis
Fluoroquinolones
Rifamycins

Cell Membrane Integrity
Polymyxin B

Metabolic Pathways (folate biosynthesis)
Sulfonamides
Trimethoprim

Protein Synthesis
Aminoglycosides
Tetracyclines
Macrolides
Chloramphenicol
Lincosamides
Oxazolidinones
Streptogramins

Energy Synthesis
**TMC207**

**In vitro:**
- Active on DS-TB, MDR-TB and XDR-TB
- Target mycobacterial ATP synthase
- First drug to interfere with energy production
- Kills non-replicating and replicating bacilli

**In mice:**
- Shortens treatment duration of DS TB from 6 to 4 months when added to SOC
- Shortens treatment duration of MDR TB from 24 to 6 months when added to SOC

**In patients:**
- Proof-of-Principle in one week early bactericidal activity (EBA) trial
- Increases culture conversion by \( \sim 40\% \) in MDR TB patients (8 week trial)
TMC207 (R207910): diarylquinoline
A new class of TB drug

- Novel MoA: selectively active against Mycobacteria
- Active against multidrug-resistant strains
- Metabolized by CYP3A4
  - No inhibition or induction of CYP3A4 in vitro
- Potent activity in mouse models
  - Bactericidal efficacy
  - Sterilizing efficacy
  - Ability to shorten treatment duration
- Safe and well-tolerated in healthy volunteers
- Potential to address major unmet needs in TB
TMC207: similar activity in drug susceptible TB and MDR TB

TMC207 accelerates the drop in bacterial load when added to SOC

- Bacterial load in lungs of mice after 1 month of therapy (yellow bars) or after 2 months of therapy (blue bars)
- Drugs administered 5x/week:
  - R, rifampin (10 mg/kg)
  - J, TMC207 (25 mg/kg)
  - H, isoniazid (25 mg/kg)
  - Z, pyrazinamide (150 mg/kg)
- Significant differences (P<0.0018) between
  - RHZ and any combination containing TMC207 after 1 month
  - RHZ and the RJZ and RHZJ after 2 months

SOC, standard of care

Established murine model of TB infection

5 log drop in 4 weeks
TMC207 accelerates the drop in bacterial load when added to SOC for MDR TB

- Bacterial load in lungs of mice after 1 month of therapy (orange bars) or after 2 months of therapy (blue bars)
- Drugs administered 5x/week:
  - H, isoniazid (25 mg/kg)
  - R, rifampin (10 mg/kg)
  - Z, pyrazinamide (150 mg/kg)
  - J, TMC207 (25 mg/kg)
  - A, amikacin (150 mg/kg)
  - Et, Ethionamide (50 mg/kg)
  - M, moxifloxacin (100 mg/kg)
- All TMC207-containing regimens were significantly more active than the non-TMC207-containing regimens (P < 0.05)

SOC, standard of care
Lounis et al., AAC 2006, 50, 3543
TMC207 clinical studies
TMC207: clinical studies

• Phase I
  – CDE 101: single ascending dose (25—700mg)
  – CDE 102: multiple ascending dose (25—400mg, 14 days)
  – CDE 103: rifampicin interaction study (CYP3A4 induction)
  – C104: isoniazid + pyrazinamide interaction study
  – C108: bioequivalence tablet vs. oral solution
  – C109: ketoconazole interaction (CYP3A4 inhibition)
  – C110: lopinavir/ritonavir interaction

• Phase II
  – C202: proof of concept, extended early bactericidal activity vs. isoniazid + rifampicin
  – C208: two stage study in patients with MDR TB
  – C209: open-label study in patients with MDR TB

(e)EBA, extended early bactericidal activity
TMC207 C208: study design

R washout

Double-blind phase

BR + TMC207

BR + placebo

BR alone

Patients with newly diagnosed sputum smear positive pulmonary MDR-TB infection

1w

8 weeks

Stage I (n=47)
- South Africa

24 weeks

Stage II (n=161)
- Brazil, Russia, India
- South Africa
- Peru
- Latvia
- Thailand
- Philippines

2 y follow-up
18-24 month total MDR-TB treatment

TMC207 regimen:
- 400 mg QD for 14 days, then
- 200 mg TIW

BR, background regimen

TMC207-C208: stage 1 conclusions

- TMC207 was safe and well-tolerated over 8 weeks

- Addition of TMC207 to a 5-drug MDR-TB regimen resulted in:
  - A significantly shorter time to culture conversion compared with placebo
    - Median 11 weeks versus 18 weeks (p=0.03)
  - A higher sputum conversion rate compared to placebo
    - 81% versus 57%

TMC207-C208: stage 2 objectives

- Demonstrate superiority of TMC207 compared to placebo at 24 weeks of treatment
  - Primary analysis: time to sputum culture conversion
    - Defined as 2 consecutive negative MGIT cultures collected at least 25 days apart and not followed by a confirmed positive culture
    - Subjects who drop out during the 24 weeks are considered failed, irrespective of their culture status at time of dropout.
  - Secondary analysis: culture conversion rates at 24 weeks

Mc Neeley DF, et al. 41st IUATLD 2010
Patients with newly and non-newly diagnosed sputum smear positive pulmonary MDR-TB infection

- 2w screening
- 24 weeks (n=225)

Open label

OBR + TMC207

TMC207 regimen:
- 400 mg QD for 14 days, then
- 200 mg TIW

OBR alone

- 1.5 y follow-up
- 18-24 month total MDR-TB treatment

Haxaire M et al. IUATLD 2011
Conclusions from study TMC207- C209

• Addition of TMC207 to an individualized MDR-TB regimen:
  • Was safe and well-tolerated
  • Resulted in an 80% culture conversion rate at week 24, with median times to culture conversion of:
    • 8 weeks for patients with MDR TB
    • 12 weeks for patients with Pre-XDR TB
    • 24 weeks for patients with XDR TB

• Responder rates were higher for:
  • Patients with no cavitations ($p^* = 0.0157$)
  • Patients with lower extent of resistance ($p^* = 0.0006$)
  • Patients on 3 or more potentially active drugs in their BR ($p^* = 0.0376$)

* Cox proportional hazards model

Haxaire M et al. IUATLD 2011
Muchas gracias