PK and Drug Interactions in a Changing World: New Drugs for TB and New Regimens for TB-HIV Co-infection

Charles Flexner, MD
Johns Hopkins University
What have we learned about TB pharmacology?

Drug concentrations matter!
Association of rifabutin AUC with TBC treatment response

Weiner et al., *CID* 2005; 40: 1481
What have we learned about TB pharmacology?

Drug interactions can - and will - occur!
HIV Drug Interactions in the Global Community

- New diseases
  - Tuberculosis

- New cultures
  - Traditional and herbal medicines

- New formulations
  - Impact of generics, co-formulations

- New families
  - Drug interactions and contraceptives

- New populations
  - Do genetics and ethnicity matter?
Treatment of the TB/HIV Co-infected Patient
The problem:

- Rifampin, rifapentine, or rifabutin are key components of most anti-TB regimens.
- All three drugs are inducers of drug metabolizing enzymes.
- How broad is their potential for producing clinically significant drug-drug interactions?
Example:

Possible metabolic drug interactions involving rifapentine and moxifloxacin
Rifapentine: the Drug

- Only new drug approved for the treatment of TB in the U.S. in the past 30 years
- Inhibits bacterial DNA-dependent RNA polymerase → inhibits RNA transcription
- Rifamycin derivative with MIC$_{50}$ and MIC$_{90}$ 1-2 fold dilutions lower than rifampin (i.e. more potent)
- Half-life 5 times longer than rifampin
- Concentrates 24-60 fold within macrophages
- Potent P450 enzyme inducer

Rifapentine plus Moxifloxacin

The problem:

- Rifapentine could induce moxifloxacin metabolism, decrease moxi concentrations, and reduce moxi’s anti-TB activity.
How rifamycins induce drug metabolizing enzymes

- Dooley et al., *J Infect Dis* 2008;198:948
Study Design: PK interactions between rifapentine and moxifloxacin

Moxi 24h PK | RPT 48h PK |

Moxi/RPT 72h PK

Rifapentine 900 mg thrice-weekly

Moxifloxacin 400 mg daily
Effect of RPT on Moxi Concentrations

RPT Concentration: single vs. multiple doses

Treatment of the TB/HIV co-infected patient

The problem:

- PK interactions between ARV’s and anti-TB drugs may or may not be clinically significant.
  - Definitive clinical studies are difficult to do
Future pharmacology priorities for new TB drugs and regimens?
Future TBC PK/PD Priority Studies?

- Clinically important questions unlikely to be studied by industry (cost, time, or priority constraints)
- Scientifically important questions of little interest to industry
- Studies involving drugs off patent or unprofitable
- Studies in special patient populations, or long-term studies in patients
Study opportunities with TMC-207:
An investigational inhibitor of mycobacterial ATP synthase
TMC-207

- A diarylquinoline with activity against drug-sensitive and drug-resistant TB, including XDR-TB.
- Inhibits the proton pump function of mycobacterial ATP synthase -- a novel mechanism of action.
- Intracellular [ATP] is significantly lower in hypoxic nonreplicating *M. tuberculosis*, which are more susceptible to ATP depletion.
- TMC-207 may be uniquely bactericidal and sterilizing for nonreplicating MTB, allowing dramatic shortening of the course of treatment.
TMC207 Human Pharmacokinetics

Van Heeswijk et al., *ICAAC* 2007; abstract A-780
TMC-207 activity against MDR-TB

- 47 patients with MDR-TB were randomized to receive a 5-drug MDR regimen (KAN+OFX+ETA+TER+PZA) plus either placebo (n=24) or TMC207 (n=23) for 8 weeks and then continued with the MDR regimen.

- Efficacy assessment at 8 weeks:
  - By serial sputum colony counting: 0/9 TMC207-treated patients culture-positive versus 9/13 patients in the control group.
  - By MGIT tubes: 47.5% of TMC207 treated patients became culture negative versus 8.7% treated with placebo (p=0.003)

- Diacon et al., 48th ICAAC, 2008, Washington, DC, LB Abstract
Culture conversion in liquid media

Diacon et al., *ICAAC* 2008; LB abstract
ACTG Protocol 5267: Safety, Tolerability, and Pharmacokinetic Interaction Study of Single Dose TMC207 and Efavirenz in Healthy Volunteers

Kelly Dooley, Susan Swindells, David Haas, Jeong-Gun Park, Reena Masih, Ilene Wiggins, Francesca Aweeka, Amita Gupta, Kristy Grimm, Rolf P.G. van Heeswijk, Sonia Qasba, and Charles Flexner, for the 5267 Protocol Team
ACTG 5267 Study Design

- TMC207 & M2 336h PK (TMC alone)
- EFV 24h PK (steady state)
- TMC207 & M2 336h PK (TMC+EFV)

- TMC207 400 mg
- EFV 600 mg PO daily
What we are learning from studies of TMC-207

- Industry is willing to collaborate with government and academia on important pre-approval pharmacology studies.
- Industry is willing to provide reagents to develop investigational drug assays (pre-approval).
- Industry is still struggling to define a business model for development and marketing of new drugs for tuberculosis.
Pre- and post-exposure prophylaxis for clinical tuberculosis: a new paradigm?

- A single antibiotic with appropriate pharmacologic properties should be able to eradicate latent TB with a single dose.
  - Kill metabolically active and inactive organisms
  - Kill intracellular and extracellular organisms
  - High antimicrobial potency and low resistance
  - Very long half-life in the effect compartment
  - Wide therapeutic index

- Such an agent could make possible regional eradication of TB, similar to strategies deployed to eradicate onchocerciasis.
Acknowledgements

RPT-Moxifloxacin Studies
JHU
Kelly Dooley
Richard Chaisson
Susan Dorman
Eric Nuermerberger
Judith Hackman

NJH, Denver
Chuck Peloquin