Using *Mycobacterium tuberculosis* single nucleotide polymorphisms to predict fluoroquinolone treatment response

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A TB Patient Dies Every 18 Seconds

By the end of this talk ~50 more TB patients will have died
Introduction

• **TB treatment success rates**
  - 82% for all TB
  - 55% for MDR-TB (2016 cohort)
  - 34% for XDR-TB (2015 cohort)

• **Options for improvement of treatment success rates**
  - Novel therapies
  - Optimize current treatment
Optimizing Current Treatment

- Based on phenotypic/genotypic resistance detection
- Critical Concentration vs. clinical breakpoint
- Lost opportunity to optimize dosing

Goals of Study

Proof of Concept

• Mtb mutations can predict Fluoroquinolone MICs
• Predicted MICs can be combined with population-level PK/PD modeling to provide insights into individual dosing decisions
Methods: Isolate selection and categorization

• Clinical isolate selection
  • Archived clinical isolates from repositories in Mumbai (India), Chisinau (Moldova), Manila (Philippines) South Africa
  • Isolates were sequenced at gyrA using Pyrosequencing, Sanger, or PacBio whole genome sequencing
  • Randomly selected up to 20 isolates with the following gyrA SNPs: 88TCG, 90GTG, 91CCG, 94GGC, 94GCC, 94AAC, 94TAC, 94CAC, as well as gyrA wild types

• Isolate processing (n=138)
  • Cultured isolates and did DST with serial dilutions GFX, MFX, LFX, and OFX (~5 dilutions above critical concentration and ~3 dilutions below)

• SNP categorization into high or low MICs
  • SNPs grouped by MIC modes (wildtype, low resistance, and high resistance)
  • Differentiation was demonstrated statistically (Kruskal-Wallis test, Dunn’s test)
Methods: Population PK/PD modeling

- 10,000 patients were simulated using NONMEM
  - AUC (for each FQ) calculated based on virtual subjects PK parameters and standard PK equations
    (AUC=bioavailability*dose/clearance)
- Probability of AUC/MIC target attainment
  - Simulated using SAS 9.4 & published population PK/PD models for each FQ, linked (randomly) to SNP estimated MIC distributions
  - FQ AUC/MIC targets based on published literature

Results: SNPs categorized as high or low level resistance

A) MFX

B) GFX

C) LFX

D) OFX
Cumulative distribution plots of proportion of population likely to reach defined therapeutic targets for MFX


Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis.; 2014.
Cumulative distribution plots of proportion of population likely to reach defined therapeutic targets for MFX

MFX (target 106)
5% of low MIC pop @ 400 mg/day
44% of low MIC pop @ 800 mg/day

Low level resistance mutations (800 mg)
Low level resistance mutations (400 mg)

Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis.; 2014.
Cumulative distribution plots of proportion of population likely to reach defined therapeutic targets for MFX


Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis.; 2014.
Cumulative distribution plots of proportion of population likely to reach defined therapeutic targets for GFX

- **GFX (target 125)**
  - 22% of low MIC population at 400 mg/day
  - 59% of low MIC population at 800 mg/day
  - 73% of low MIC population at 1200 mg/day

**Wild type**
- (1200 mg)
- (800 mg)
- (400 mg)

**Low level resistance mutations**
- (1200 mg)
- (800 mg)
- (400 mg)

**High level resistance mutations**
- (1200 mg)
- (800 mg)
- (400 mg)

Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis; 2014.
Cumulative distribution plots of proportion of population likely to reach defined therapeutic targets for LFX

LFX (target 146)
4% of low MIC pop @ 750 mg/day
14% of low MIC pop @ 1250 mg/day
Cumulative distribution plots of proportion of population likely to reach defined therapeutic targets for OFX

OFX (target 100)
0% of low MIC pop @ 600 mg/day
0% of low MIC pop @ 800 mg/day
Conclusions from this Proof-of-Concept Study

• SNPs in \textit{gyrA} gene of \textit{Mtb} can be used to predict MIC distributions against individual fluoroquinolones

• SNP estimated MICs together with population PK/PD models could be used as decision support tools for rapid individualized TB treatment based on rapid molecular diagnostics

• Methods are generalizable to other antimicrobial agents which have reliable genetic markers of resistance in \textit{Mycobacterium tuberculosis}
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