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Frances Okibedi
franceo88@zedat.fu-berlin.de

Investigating alternative daily dose regimens for bedaquiline in the treatment of multidrug-resistant tuberculosis using an interactive shiny application.

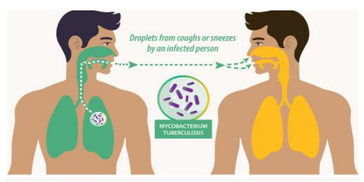
Frances Okibedi (1), Yuanxi Zou (1) and Elin M Svensson (1,2)

1 Department of Pharmacy, Uppsala University, Sweden; 2 Department of Pharmacy, Radboud Institute of Health Sciences, Radboud University Medical Center, The Netherlands

Background

Multidrug Resistance Tuberculosis (MDR-TB)

- TB is caused by MTB
- Affects mainly the lungs
- Globally 1.5/10 billion TB-related death yearly



- MDR-TB: resistance to isoniazid /rifampicin
- MDR hinders global TB control and treatment
- Cure rate for MDR-TB is lower (60%) than for DS-TB on first-line therapy (86%).
- BDQ and other new drugs improved MDR-TB treatment

The approved BDQ dose regimen

Challenges

- Different dosing frequency from QD co-administered drugs
- Missed doses can occur in TIW regimen
- Non-adherence due to long treatment time

Solution - QD BDQ Dosing

- Simplifies administration
- Maintains therapeutic QD drug levels.
- Fixed-dose combination in future.

Problem with current QD BDQ regimen

- TB Alliance 2019 study QD BDQ dose regimen
- Has been further tested in ZENIX trial
- Reaches peak concentration slower in the loading phase compared to the approved regimen

Aim: to investigate QD BDQ dose regimen with similar loading phase concentration as the approved dose regimen as well as implement a shiny app to explore different dose regimen

Methods

1. Simulation Component

Pharmacokinetic model
- Data: 2 phase IIb trials(C208, C209)
- Weight and albumin are correlated
- Age and Race are covariates
- Estimated in NONMEM

Workflow In R

2. Mrgsolve Implementation
- Model specification
- Model validation
- Dose Simulation

3. Shiny Implementation
- User interface component
- Server component
- Deployment to shinyapps.io

Dose regimen simulated
- **Approved dose regimen**
  400mg QD x2wk,200 mg TIW x22wk
- **TB Alliance dose regimen**
  200mg QD x8wk,100 mg QD x16wk
- **Proposed dose regimen**
  400mg QD x2wk,100mg QD x22wk

Results

BDQ and M2 dose regimen simulation in the shiny app

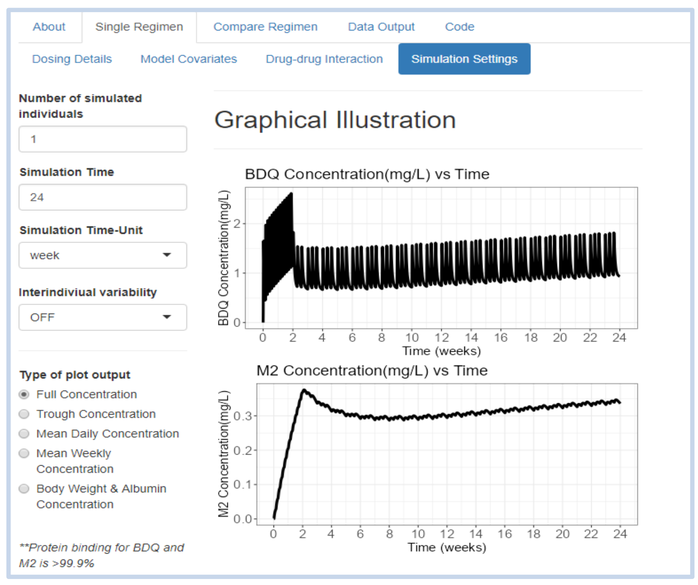


Figure 1: Approved dose typical BDQ and M2 concentration over 24 weeks

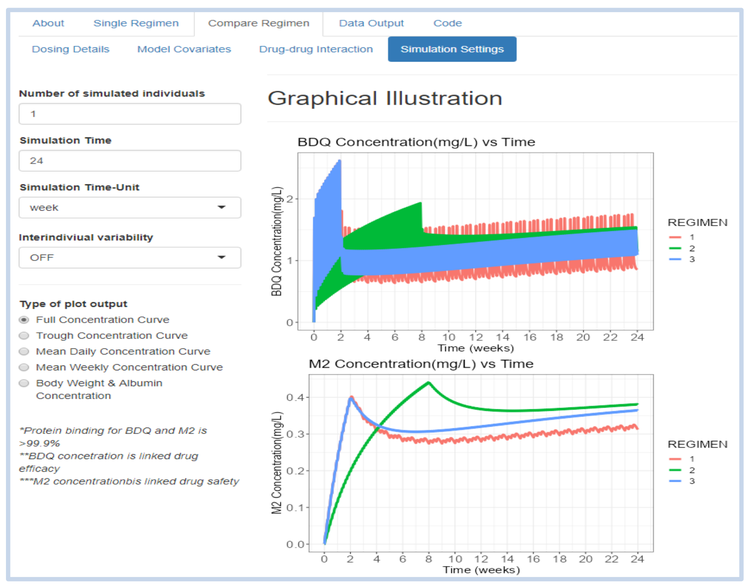


Figure 2: BDQ and M2 concentration over 24 weeks for the 3 simulated dose regimens

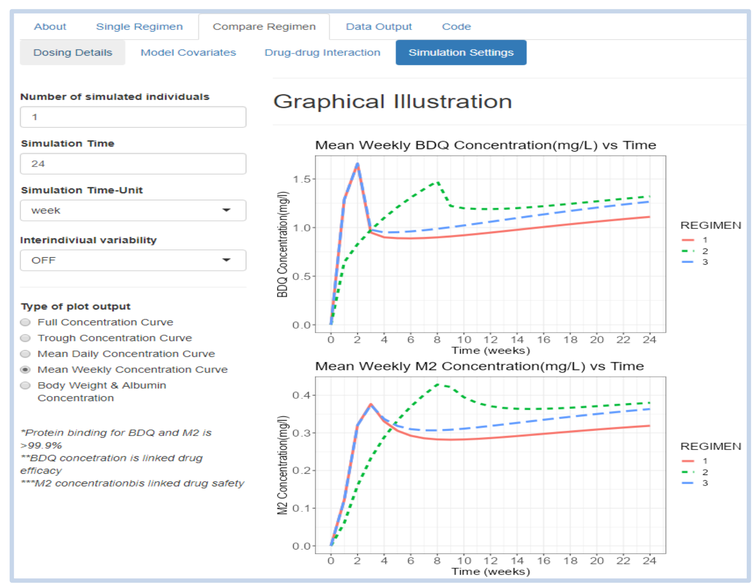


Figure 3: Mean weekly BDQ and M2 Concentration over 24 weeks for the 3 simulated dose regimens

Dose Regimen
- Approved dose: black
- 1. Approved dose: red
- 2. TB Alliance dose: green
- 3. Proposed dose: blue

- **Shiny app**:
  - Single /compare dose regimen
- **BDQ concentration**
  - linked to drug efficacy
- **M2 concentration**
  - linked to drug safety

Approved and propose dose regimen
- **At 2 weeks**
  - Same BDQ/M2 concentration
- **At 2 to 22 weeks**
  - initial decrease at start of 2 week
  - comparable increase in exposure

TB Alliance dose regimen
- **At 2 weeks**
  - lowest BDQ/M2 concentration
- **At 2 to 22 weeks**
  - peak BDQ/M2 concentration at week 8
  - highest BDQ/M2 concentration at week 24

Conclusion

The developed shiny app will enable easy exploration of alternative BDQ regimens, the impact of drug-drug interactions and covariates. The new proposed QD dose had similar BDQ and M2 concentrations as the approved dose regimen throughout the treatment period at the maintenance phase and could be tested in clinical trials.

References

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Abbreviations: *TB, Tuberculosis; MTB, Mycobacterium Tuberculosis; MDR, Multidrug Resistant; QD, Daily; TIW, Trice weekly, PK, Pharmacokinetics; BDQ, bedaquiline; NONMEM, Non-linear mixed effect modeling; M2, N-monodesmethyl metabolite; wk, week; DS-TB, Drug-susceptible Tuberculosis;*

Scan to see shiny app

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