The importance of pharmacokinetics/pharmacodynamics assessment in Phase IIB/III trials for MDR-TB treatment

Martson, A. G.; Kim, H. Y.; Marais, B.; Alffenaar, J. W.

Published in:
International Journal of Tuberculosis and Lung Disease

DOI:
10.5588/ijtld.21.0072

Publication date:
2021

INT J TUBERC LUNG DIS 25(5):336–339

http://dx.doi.org/10.5588/ijtld.21.0072

EDITORIAL

The importance of pharmacokinetics/pharmacodynamics assessment in Phase IIB/III trials for MDR-TB treatment

MULTIDRUG-RESISTANT TB (MDR-TB) TREATMENT outcomes are poor due to reduced potency of the drugs used, and because treatment adherence is affected by the prolonged duration of treatment and frequent adverse drug reactions.[1] In the absence of adequate randomised controlled trials, observational data and pooled analysis have been used for the development of MDR-TB treatment guidelines.[2] The traditional approach includes the use of at least five active drugs based on drug susceptibility testing (DST) for a treatment duration of at least 18 months, although shorter treatment options have recently been endorsed.[3]

To optimise TB patient outcomes, there has been an increased focus on patient-centred care.[4] Truly personalised treatment includes optimal drug selection based on DST results,[5] but also optimisation of drug dose and drug exposure in relation to pathogen susceptibility.[6] More information on the optimal relation between drug exposure and *Mycobacterium tuberculosis* susceptibility has become available since the early 2000s.[7] In vitro and observational studies have shown that achieving pharmacokinetics/pharmacodynamics (PK/PD) targets is important for treatment efficacy and the prevention of acquired resistance.[7] The reason why it is important to assess PK/PD in Phase IIb/III studies is because these studies are powered to evaluate treatment outcome and are therefore perfectly suited to link outcomes to PK/PD rather than theoretical 'target attainment' derived from small scale PK studies.[8] However, PK/PD measures are rarely, if ever, included in randomised controlled Phase IIb/III clinical trials to assess their contribution to treatment response.

Here, we wanted to assess the extent to which PK/PD evaluations are included in randomised controlled Phase IIb/III clinical trials, and to highlight why this is important for improving the safety and effectiveness of TB treatment, especially for drug-resistant TB.

EVIDENCE OF PK/PD EVALUATION DONE IN RANDOMISED CONTROLLED PHASE IIB/III MDR-TB TREATMENT TRIALS

A systematic search was performed using PubMed and Embase to identify any relevant articles published between January 2010 and January 2021. The search criteria included the following key words: MDR-TB, treatment, randomised controlled trial. Title and abstract screening and study selection were performed by two authors independently (AGM, JWA). Articles reporting on vaccines or immunotherapy were excluded. Conference proceedings were excluded. Full-text articles and associated online supplements, including trial protocols, were reviewed for PK/PD assessment. Data were extracted for each trial, including information about investigational drugs, study design, randomisation, blinding, outcomes and information on PK data collection and analysis.

WHAT DOES THE EVIDENCE SUGGEST?

We identified a total of 116 articles, of which 16 were selected based on title and abstract. After full text scrutiny, only six studies met the inclusion criteria. The reasons for excluding articles initially selected from the abstract were as follows: inappropriate study design ($n = 4$), conference proceedings ($n = 2$), different patient population (drug-susceptible TB), no access to full text even after contacting the corresponding author, article in Chinese language and sub-analysis of an already included study. The six randomised controlled trials evaluated the following TB drugs: moxifloxacin (MFX) ($n = 2$),[9,10] levofloxacin (LVX),[9] bedaquiline (BDQ),[11] linezolid (LZD)[12] and delamanid (DLM) ($n = 2$).[13,14] Three of the trials were open-label, and three used a double-blind design. The primary outcome of all these studies was culture conversion at various time points after initiation of treatment. Sputum culture conversion at 2 months of treatment was used in the studies on LZD[12] and DLM.[14] The study comparing MFX and LVX used sputum culture conversion at 3 months.[9] Evaluation was done at 4 and 6 months in the studies evaluating BDQ[11] and DLM.[13] PK data were collected for all subjects in three of the studies,[10,13,14] and in a subset of the subjects in one of the studies.[11] None of three studies collecting data in all of the subjects included PK data in the analysis of the primary endpoint. Three of the studies included were sponsored by a pharmaceutical company,[11,13,14] and three were investigator-initiated with governmental funding.[9,10,12] An overview of the studies is presented in the accompanying Table.[9–14]

Article submitted 2 February 2021. Final version accepted 4 February 2021.

Table Randomised controlled trials and inclusion of PK/PD information

Reference	Drug	Design	Population	*n*	Intervention	Comparison	Outcome	PK data collected	PK data included*
9	MFX, LVX	Open-label, multicentre	Pulmonary MDR-TB	182	MFX 400 mg ($n = 77$)	LVX 750 mg ($n = 78$)	Sputum-culture conversion after 3 months of treatment	Protocol not published	No
10	MFX	Open label, multicentre	Pulmonary MDR-TB	383 (2:1)	MFX dosed according to body-weight category ($n = 253$)	Conventional regimen with MFX dosed at 400 mg ($n = 130$)	Sputum cultures negative at 132 weeks or unfavourable outcome	Yes	No
11	BDQ	Double-blind, placebo-controlled	Pulmonary MDR-TB	132 (1:1)	BDQ + background regimen	Placebo + background regimen	Time to sputum-culture conversion The primary analysis was based on 24 weeks	Yes	No
12	LZD	Open-label, multicentre	Pulmonary XDR-TB	65	LZD + background regimen	Background regimen	Sputum-culture conversion over 2 months (taken at least 30 days apart)	Protocol not published	No
13	DLM	Double-blind, placebo-controlled	Pulmonary MDR-TB	327 (2:1)	DLM 100 mg twice daily + background regimen	Placebo twice daily + background regimen	Sputum-culture conversion over 6 months	Yes	No
14	DLM	Double-blind, placebo-controlled, multicentre	Pulmonary MDR-TB	402 (1:1:1)	DLM 100 mg twice daily DLM 200 mg twice daily + background regimen	Placebo twice daily + background regimen	Sputum-culture conversion at 2 months	Yes	No

* PK data included in the analysis of the primary endpoint.
PK = pharmacokinetics; PD = pharmacodynamics; MFX = moxifloxacin; LVX = levofloxacin; MDR-TB; multidrug-resistant TB; BDQ = bedaquiline; LZD = linezolid; XDR-TB = extensively drug-resistant TB; DLM = delamanid.

DETAILS OF PK/PD ASSESSMENTS PERFORMED

The study by Gler et al. compared sputum culture conversion at 2 months of DLM in a dose of 100 mg twice daily, 200 mg twice daily with placebo on top of a background drug regimen.[14] The following PK parameters were included: time to maximum plasma concentration (t_{max}), maximum (or peak) concentration (C_{max}), area under the plasma concentration-time curve over the last 24-h dosing interval ($AUC_{0–24h}$), ratios of accumulation for C_{max} and $AUC_{0–24h}$ on Days 1, 14, 28 and 56.[14] On these days, the samples were collected pre-dose and 2, 3, 4, 10, 12, 14 and 24 h after the morning dose. The sample analysis included both DLM and its metabolites.

The study by von Groote-Bidlingmaier et al. evaluated the same DLM dosing regimen but assessed sputum culture conversion at 6 months after treatment initiation.[13] Blood sampling for DLM and metabolites were also included in the study protocol.[13] The sampling was preformed pre-dose and randomly between 2 and 8 h after dose intake from Week 3 onwards.

The study by Diacon et al. compared the difference in sputum culture conversion between BDQ and placebo on top of a background drug regimen.[11] The study was divided into two stages: 50 patients were planned to be enrolled in the first stage and 150 in the second stage. Data for a full PK curve were collected (pre-dose and 1, 3, 5, 6, 8, 12, 24 h after dose) for BDQ and metabolite M2 in both treatment groups at Week 2 (Stage 1 patients and a subset of approximately 50 Stage 2 subjects). Subsequently, pre-dose sampling was continued weekly up to Week 8 and at Weeks 10, 12, 16, 24, 36, 48, 72, 84 and 104 for Stage 1 subjects and at Weeks 28, 32, 36, 48, 60, 72, 84, 96 and 120 for Stage 2 subjects.[11]

The study by Nunn et al. compared a short regimen of 9–11 months, including a high dose of MFX, with the traditional longer treatment of 20 months with a standard dose of MFX.[10] The study protocol mentioned that individual PK parameters would be calculated for each patient.[10] These were derived from individual plasma concentrations: C_{min}, C_{last} (the last measurable plasma concentration), t_{last} (time of the last measurable plasma concentration) and AUC_{tau} (the area under the concentration-time curve from time of administration to the end of the dosing interval). The PK sampling included a pre-dose sample at randomisation and at Weeks 2, 4, 16, 24, 32, 40, and post dose at Weeks 2, 12, 24 and 40. In addition to the evaluation of MFX the PK/PD relationships between BDQ concentrations and efficacy/safety were scheduled to be analysed.

MOTIVATION FOR INCLUDING PK/PD DATA IN OUTCOME ASSESSMENT

Three of the six (67%) Phase IIb/III clinical trials on pulmonary multidrug- and extensively drug-resistant TB (MDR/XDR-TB) collected PK data in all subjects, but did not include this information in the analysis of the primary study outcomes, despite having the data to hand.

The PK/PD (e.g., AUC/minimum inhibitory concentration [MIC]) of the evaluated drugs (i.e., fluoroquinolones, LZD and BDQ), except for DLM,[15] were studied using in vitro and in vivo infection models, as well as human studies evaluating the early bactericidal effect. Studies on the PK of these drugs have shown significant variability in drug exposure.[7] Already in 2004, a higher MFX dose of 800 mg once daily had been suggested using a hollow fibre infection model and subsequent Monte Carlo simulations.[16] Moreover, targeting *f*AUC/MIC in MFX therapy has been proposed to be used in clinical care for specific patients.[17] LVX therapy should also be guided by targeting AUC/MIC, and therapeutic drug monitoring is suggested when MIC $\geq$ 0.5 mg/L is observed[18] to maximise antimicrobial kill and prevention of resistance.[19] Lower LZD doses of 600 mg once daily have been proposed to reduce toxicity while attaining optimal AUC/MIC targets to maximise bactericidal effect and avoid resistance, and this was proposed for testing in prospective studies.[20–23] In addition, optimal kill has been associated with well described *f*AUC/MIC[21,23] ratios.

PK/PD data for BDQ are limited. However, using the data from the clinical trials, the exposure-response relationship has been described using non-linear, mixed effects modelling.[24] This can guide further studies when dose optimisation is considered. Awareness of acquired BDQ resistance[25] and variability in BDQ exposure in selected patients[26] is important. In addition, dose optimisation of fluoroquinolones is essential for effective implementation of all-oral, short-course treatment regimens for rifampicin-resistant/MDR-TB in order to achieve the best treatment outcomes and to protect against the very real threat of acquired BDQ resistance,[27] which would be a global catastrophe if linked to secondary transmission and clonal spread of these resistant strains.

It is apparent that PK/PD analysis, even when the data have been collected, has not yet found its way into primary endpoint analysis. Although in vitro PK/PD infection models have been endorsed for dose selection of clinical trials,[28] published data clearly show the disconnect between preclinical models and Phase II/III studies.[29] It is important to embed PK/PD assessment into the prospective study designs of TB treatment for adults and children.[7,8,30] To increase feasibility, limited sampling strategies in combination with population PK modelling can be used. This will reduce the number of samples to be collected per patient, thereby reducing the burden for patient and staff, as well as costs, including the total number of samples to be analysed in the laboratory. Fortunately, new initiatives have been setup (e.g., Pharmacokinetic and pharmacodynamic study of high-dose rifapentine and moxifloxacin for treatment of tuberculosis, NCT02563327) to incorporate PK/PD into the design and primary analysis of Phase IIb/III studies. With better PK/PD, drug susceptibility, disease severity and markers of treatment response data, the factors associated with optimal clinical outcomes could be better interrogated[31] to inform guidelines on how best to improve people-centred TB care.

A-G. Märtson[1]
H. Y. Kim[2,3,4]
B. Marais[4,5,6]
J-W. Alffenaar[2,3,4]
[1]Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands;
[2]Faculty of Medicine and Health, School of Pharmacy, University of Sydney, Sydney, NSW,
[3]Westmead Hospital, Westmead, NSW,
[4]Marie Bashir Institute for Infectious Diseases and Biosecurity, University of Sydney, Sydney, NSW,
[5]Faculty of Medicine and Health, School of Medicine, University of Sydney, Sydney, NSW,
[6]Children's Hospital at Westmead, Westmead, NSW, Australia
Correspondence to: J W C Alffenaar, Faculty of Medicine and Health, School of Pharmacy, University of Sydney, Pharmacy Building (A15), NSW 2006, Sydney, Australia. email johannes.alffenaar@sydney.edu.au

Acknowledgements

The article is part of the activities of the TB Pharmacology Committee, Global Tuberculosis Network. A-GM was funded by Marie Skłodowska-Curie Actions, Brussels, Belgium (grant agreement no. 713660-PRONKJEWAIL-H2020-MSCA-COFUND-2015).

Conflicts of interest: none declared.

References

1 World Health Organization. Global tuberculosis report, 2019. Geneva, Switzerland: WHO, 2019.
2 Ahmad N, et al. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. Lancet 2018; 392(10150): 821–834.
3 World Health Organization. WHO consolidated guidelines on drug-resistant tuberculosis treatment. Geneva, Switzerland: WHO, 2019. https://www.who.int/tb/publications/2019/consolidated-guidelines-drug-resistant-TB-treatment/en/.
4 Kendall EA, et al. What will it take to eliminate drug-resistant tuberculosis? Int J Tuberc Lung Dis 2019; 23(5): 535–546.
5 Talbot EA, Pai M. Tackling drug-resistant tuberculosis: we need a critical synergy of product and process innovations. Int J Tuberc Lung Dis 2019; 23(7): 774–782.

6 Lange C, et al. Management of patients with multidrug-resistant tuberculosis. Int J Tuberc Lung Dis 2019; 23(6): 645–662.
7 Alffenaar J-WC, et al. Integrating pharmacokinetics and pharmacodynamics in operational research to end tuberculosis. Clin Infect Dis 2020; 70(8): 1774–1780.
8 Märtson A-G, et al. How to design a study to evaluate therapeutic drug monitoring in infectious diseases? Clin Microbiol Infect 2020; 26(8): 1008–1016.
9 Koh W-J, et al. Comparison of levofloxacin versus moxifloxacin for multidrug-resistant tuberculosis. Am J Respir Crit Care Med 2013; 188(7): 858–864.
10 Nunn AJ, et al. A trial of a shorter regimen for rifampin-resistant tuberculosis. N Engl J Med 2019; 380(13): 1201–1213.
11 Diacon AH, et al. Multidrug-resistant tuberculosis and culture conversion with bedaquiline. N Engl J Med 2014; 371(8): 723–732.
12 Tang S, et al. Efficacy, safety and tolerability of linezolid for the treatment of XDR-TB: a study in China. Eur Respir J 2015; 45(1): 161–170.
13 von Groote-Bidlingmaier F, et al. Efficacy and safety of delamanid in combination with an optimised background regimen for treatment of multidrug-resistant tuberculosis: a multicentre, randomised, double-blind, placebo-controlled, parallel group phase 3 trial. Lancet Respir Med 2019; 7(3): 249–259.
14 Gler MT, et al. Delamanid for multidrug-resistant pulmonary tuberculosis. N Engl J Med 2012; 366(23): 2151–2160.
15 Nguyen TVA, et al. Delamanid resistance: update and clinical management. Clin Infect Dis 2020; 71(12): 3252–3259
16 Gumbo T, et al. Selection of a moxifloxacin dose that suppresses drug resistance in *Mycobacterium tuberculosis*, by use of an in vitro pharmacodynamic infection model and mathematical modeling. J Infect Dis 2004; 190(9): 1642–1651.
17 Pranger AD, et al. Evaluation of moxifloxacin for the treatment of tuberculosis: 3 years of experience. Eur Respir J 2011; 38(4): 888–894.
18 Ghimire S, et al. Pharmacokinetic/pharmacodynamic-based optimization of levofloxacin administration in the treatment of MDR-TB. J Antimicrob Chemother 2016; 71(10): 2691–2703.
19 Deshpande D, et al. Levofloxacin pharmacokinetics/pharmacodynamics, dosing, susceptibility breakpoints, and artificial intelligence in the treatment of multidrug-resistant tuberculosis. Clin Infect Dis 2018; 67(Suppl 3): S293–S302.
20 Heinrichs MT, et al. Dose optimization of moxifloxacin and linezolid against tuberculosis using mathematical modeling and simulation. Int J Antimicrob Agents 2019; 53(3): 275–283.
21 Srivastava S, et al. Linezolid dose that maximizes sterilizing effect while minimizing toxicity and resistance emergence for tuberculosis. Antimicrob Agents Chemother 2017; 61(8): e00751-17.
22 Millard J, et al. Linezolid pharmacokinetics in MDR-TB: a systematic review, meta-analysis and Monte Carlo simulation. J Antimicrob Chemother 2018; 73(7): 1755–1762.
23 Bolhuis MS, et al. Linezolid-based regimens for multidrug-resistant tuberculosis (TB): a systematic review to establish or revise the current recommended dose for TB treatment. Clin Infect Dis 2018; 67(Suppl 3): S327–S335.
24 Svensson EM, Karlsson MO. Modelling of mycobacterial load reveals bedaquiline's exposure-response relationship in patients with drug-resistant TB. J Antimicrob Chemother 2017; 72(12): 3398–3405.
25 Nguyen TVA, et al. Bedaquiline resistance: its emergence, mechanism, and prevention. Clin Infect Dis 2018; 66(10): 1625–1630.
26 Alffenaar J-WC, et al. Should we worry about bedaquiline exposure in the treatment of multidrug-resistant and extensively drug-resistant tuberculosis? Eur Respir J 2020; 55(2).
27 Cox V, et al. Clinical perspectives on treatment of rifampicin-resistant/multidrug-resistant TB. Int J Tuberc Lung Dis 2020; 24(11): 1134–1144.
28 Romero K, Clay R, Hanna D. Strategic regulatory evaluation and endorsement of the hollow fiber tuberculosis system as a novel drug development tool. Clin Infect Dis 2015; 61 (Suppl 1): S5–S9.
29 Alffenaar JWC, Gumbo T, Aarnoutse R. Shorter moxifloxacin-based regimens for drug-sensitive tuberculosis. N Engl J Med 2015; 372(6): 576–577.
30 Seddon JA, et al. Conducting efficacy trials in children with MDR-TB: what is the rationale and how should they be done? Int J Tuberc Lung Dis 2018; 22(5): 24–33.
31 Dooley KE, et al. Advancing the development of new tuberculosis treatment regimens: The essential role of translational and clinical pharmacology and microbiology. PLoS Med 2019; 16(7): e1002842.