

The Impact of First-Line Anti-Tubercular Drugs' Pharmacokinetics on Treatment Outcome: A Systematic Review

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Background: Tuberculosis remains the major public health problem besides tremendous efforts to combat it. Most tuberculosis patients are treated with a standard dose of first-line anti-TB drugs. The cure rate, however, varies from patient to patient. Various factors have been related to anti-TB treatment failure. In recent years, studies associating lower plasma concentrations of anti-TB drugs with poor treatment outcomes are emerging although the results are inconclusive.

Objective: Investigate the impact of first-line anti-tubercular drugs pharmacokinetics on treatment outcome.

Methods: A systematic search of Pubmed, EMBASE, Web of Science, and the Cochrane Library for articles published in the English language between January 2010 to June 2020 was conducted to identify eligible studies describing associations of first-line anti-tubercular drug pharmacokinetics with treatment outcomes. The primary outcomes considered were pharmacokinetics parameter results and its association with treatment outcome.

Results: The search identified 1754 articles of which twelve articles; ten prospective observational studies and two controlled clinical trials fulfilled the eligibility criteria. The majority of the studies showed target concentrations for the first-line anti-tubercular drugs below the current standard range. Among the twelve studies, eleven studies assessed rifampicin pharmacokinetics of which eight reported association of drug concentration and treatment outcomes. Similarly, four out of eight and three out of seven reported drug concentration and treatment outcome association for isoniazid and pyrazinamide, respectively. Despite the low plasma concentration, a favorable treatment outcome was achieved for the bulk of the patients. Irrespective of the inconsistency, an increase in exposure to rifampicin improved the outcome, and lower rifampicin, isoniazid, and pyrazinamide concentration are associated with poor outcome. No data are available for ethambutol associating its pharmacokinetics with treatment outcomes.

Conclusion: The pharmacokinetics of first-line antitubercular drugs can influence treatment outcomes. Further controlled clinical studies are, however, required to establish these relationships.

Keywords: tuberculosis, pharmacokinetics, treatment outcomes, anti-TB drugs

Introduction

Tuberculosis (TB), an infectious disease caused by *Mycobacterium Tuberculosis*, stays the main health problem globally. TB is one of the top 10 causes of death and the leading cause of death from infectious diseases worldwide. According to the world health organization (WHO) 2019 tuberculosis report, TB caused an estimated

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1.2 million deaths among HIV-negative people and 251 000 deaths among HIV positive people in 2018.¹ The aspiring strategy of WHO to END TB aims to reduce TB incidence and mortality in 2035 by 90%, and 95%, respectively compared to the 2015 cases.² The first line anti-TB drugs which include rifampicin (RMP), isoniazid (INH), pyrazinamide (PZA), and ethambutol (EMB) have a cure rate of up to 95% in early clinical trials,³ but the success rates drop as low as 65% in some areas.⁴ Drug resistant TB poses a key threat to control TB globally with the first-line drugs. For example, the incidence of multi-drug resistance (MDR-TB) and extensive multi-drug resistance (XDR-TB) is increasing over time, for instance, 484,000 cases of MDR-TB cases were reported in 2018 which could decrease the success achieved.²

Many factors might be associated to treatment failure. Health factors such as HIV infection, diabetes mellitus, low body weight, cavitation on chest x-ray, high bacterial burden, drug resistance, positive culture after two months of treatment; and sociodemographic factors like drug abuse, alcoholism, smoking, and poor treatment adherence were reported in several studies.^{5–10} Data from mice,¹¹ and hollow fiber system (HFS) models,¹² emphasized pharmacokinetic studies to predict tuberculosis treatment outcome. Furthermore, WHO recognized pharmacokinetics (PK) and pharmacodynamics (PD) studies to play a key role to establish the most appropriate dose of anti-TB medications.¹³

PK describes the time course of a drug concentration in different body compartments, such as blood, plasma, brain, lungs, and other tissue. It deals with what the body does to the drug; absorption, distribution, metabolism, and excretion.¹⁴ Poor compliance to treatment has been considered as the major cause for treatment failure in tuberculosis treatment historically.¹⁵ However, in recent years, several studies associated low serum concentrations of anti-TB drugs with poor treatment outcomes. The reference range for various first-line anti-TB drugs with therapeutic cut-offs is given in Table 1.¹⁶ PK parameters especially the total exposure to anti-TB drugs (the area under the plasma concentration vs time curve (AUC₀₋₂₄) and/or the peak plasma concentration (C_{max}) appear to be relevant for anti-TB drugs.¹⁷

Systematic reviews and meta-analyses describing relations of PK and treatment outcome have been published previously.^{18–22} However, the objectives and conclusions of these reviews or meta-analyses were not consistent (Table S1). For example, Pasipanodya et al reviewed the

Table 1 Basic Pharmacokinetics of First-Line Anti-Tubercular Drugs¹⁶

Drug Name	Dose	Serum C _{max} (µg/mL)	T _{max} (hr)	Serum T _{1/2} (hr)
Rifampicin	600mg	8–24	2	2–3
Isoniazid	300mg	3–6	0.75–2	1.5 fast 4 slow
Pyrazinamide	25–35mg/kg	20–60	1–2	9
Ethambutol	25mg/kg	2–6	2–3	Biphasic: 2–4, then 12–14

shreds of evidence on the association of isoniazid pharmacokinetic variability with either microbiological failure or acquired drug resistance and concluded pharmacokinetic variability of isoniazid was significantly associated with failure of therapy and acquired drug resistance in patients.¹⁸ However, reviews focused on the association of drug concentration and treatment outcomes have contradicting conclusions. Perumal et al have shown that low PZA concentration probably increased the risk of poor outcomes; low RMP concentration might slightly increase the risk of poor outcomes; whereas low concentrations of INH and EMB had no clear effect on the treatment outcome.²² On another hand, Sekaggya-Wiltshire et al and Wilby et al failed to reach on a conclusion that plasma concentration of first-line anti-tubercular drugs affects treatment outcome.^{19,21}

In addition to variation in the conclusion, the majority of the previously published reviews included all types of studies ranging from controlled clinical trials to case reports leading to a varying degree of evidence.²³ This systematic review was, therefore, designed to evaluate the recent evidence on the effects of pharmacokinetics in particular plasma concentration on tuberculosis treatment outcome by reviewing only prospective cohort studies and randomized clinical trials that have a better level of evidence.

Methods

Literature Search Strategy

We conducted the review according to the Preferred Reporting Items for Systematic Reviews (Table S2) and Meta-Analyses (PRISMA) statement. The protocol was registered at PROSPERO (Registration number CRD42019138544).²⁴

We identified studies among tuberculosis patients in which all or any of the first-line anti-tubercular drug pharmacokinetic data or drug concentration and tuberculosis treatment outcomes were reported. A systematic search of Pubmed, EMBASE, and Web of Science for articles published in the English language over the last ten years (January 1, 2010- June 8, 2020) was done. We applied the search strategy including the next terms: “antitubercular agents” OR antituberculosis OR antimycobacterial, OR Isoniazid OR Pyrazinamide OR Rifampicin OR Rifampin OR Ethambutol AND “pharmacokinetics” or “concentration” AND “treatment outcomes” OR “sputum conversion” OR “culture conversion”. We hand search reference lists from relevant studies, to identify further eligible articles not found by the systematic search. The search included only adult human studies.

Eligibility Criteria

The following inclusion criteria were used to select studies: patients (15 years and above) and treated with first-line anti-tubercular drugs (INH, RMP, PZA, and EMB) according to WHO treatment guidelines and at least one of whose PK data described. Only prospective cohort studies and controlled clinical trials were included. However, studies reporting pharmacokinetics effect on treatment outcome in children were excluded. Besides, population modeling, review article, retrospective studies, case-control, and case series studies were excluded. There is no limitation based on gender and other socio-demographic characteristics of study participants.

Data Quality Assessment

The included study quality was assessed using appropriate tools. Blended Cochrane’s Risk of Bias assessment of Randomized Controlled Trials for controlled clinical trial studies with the Newcastle-Ottawa Quality Assessment Scale for cohort studies was used to assess the quality of the included studies. Quality assessment of the studies was done by one author (TS) using the prepared checklist (Table S3).

Data Extraction

A pre-designed data extraction form was used to review relevant studies (Table S4). Two authors (TS and ET) independently extracted data. Included articles were read and screened for eligibility criteria. From the studies included in the review, data were collected on study design, participant characteristics, pharmacokinetic

parameters (Cmax, AUC or Cmax/MIC, AUC/MIC), treatment outcomes (cure, relapse, failed, culture conversion, smear conversion), the correlation between PK parameters, and treatment outcomes. The pharmacokinetics parameter results and its’ association with treatment outcome were the primary outcomes considered strictly during data extraction for each study included. Disagreements between the two reviewers during data extraction were resolved through discussion. Similarly, if any ambiguity on the study methods or results was encountered the two reviewers discussed the issue together and resolved the ambiguity. No synthesis of data was done and contact of authors was not found to be relevant during the review for original data.

Results

Study Characteristics

As shown in Figure 1, a total of 1754 articles was identified. Of which, 47 duplicates and 1665 articles evaluated by their titles and abstracts were excluded. The remaining 42 studies were further evaluated through the full reading of their texts. 30 studies were excluded further because they are either review article, population pharmacokinetic modeling, retrospective studies, not having treatment outcome reported, or lack of pharmacokinetics data either AUC, Cmax, or both. The remaining 12 studies were selected for the final qualitative analysis. The geographic location of the included studies was; six from Africa,^{25–30} one from Europe,³¹ two from Latin America,^{32,33} and the remaining three from Asia.^{34–36} The majority of the studies were observational prospective in design. Only two of the studies included in this review were randomized clinical trials as shown in Table 2.^{30,32} The median (mean) age of study participants ranges from 25 to 42. In all studies, some participants had comorbid conditions; either HIV or diabetes mellitus.^{29,33–36} The PRISMA Flow diagram is shown in Figure 1.

Quality of Included Studies

All studies were assessed for the following parameters; 1. Representativeness of the selected cohorts (treatment of tuberculosis was with first-line anti-tubercular drugs) 2. The outcome of interest was not presented at the start of the study (no reported drug resistance at the beginning of treatment) 3. Compatibility of study participant 4. Assessment of outcome (treatment outcome listed above) 5. Adequacy of the duration of follow-up (at least for two

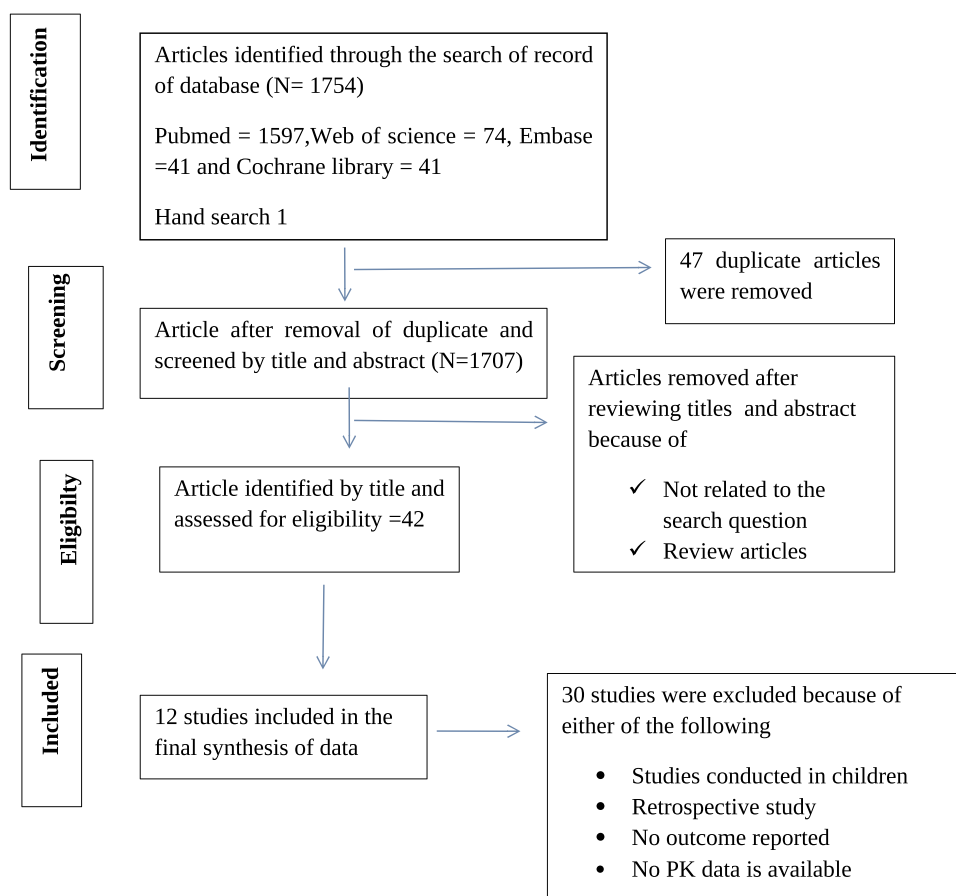


Figure 1 PRISMA flow diagram showing the literature search for studies which described drug pharmacokinetics of first line tuberculosis drugs and treatment outcomes. **Notes:** PRISMA figure adapted from Liberati A, Altman D, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Journal of Clinical Epidemiology*. 2009;62(10). Creative Commons.

Abbreviations: PK, pharmacokinetics; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

months) and for controlled randomized clinical trials, a randomization process was considered. Ten of the twelve studies were observational prospective studies. As shown in Table 2 all prospective observational studies have a low risk of bias. Similarly, in the remaining two randomized controlled clinical trials, although the proportion of patients with low PK and poor treatment outcomes was not indicated, they had a low risk of bias.

Pharmacokinetic Data and Treatment Outcome

Among the twelve studies evaluating PK parameters with treatment outcome, four assessed RMP only,^{26,27,30,32} one INH only,³³ five three drugs (RMP, INH, and PZA)^{25,29,34–36} and two all drugs (RMP, INH, PZA, EMB).^{28,31} All studies reported clinical outcomes and their association with some kind of pharmacokinetics parameters. However, the proportion of patients with a low level of drug concentration was

not reported in four studies.^{27,30,32,36} Eight studies reported the proportion of study participants who had low plasma concentration. Strikingly, in one study, 100% of participants have low plasma C_{max} measured at 2.5-hour post-dose.²⁶ In the majority of the studies that reported plasma levels of the drug, a large percentage of participants had a lower plasma concentration of RMP (up to 91%) and INH (up to 88%). However, the PZA level seems better in plasma availability (Table 3). Studies varied considerably at the time of blood sampling. This ranged from single-point sampling; at 2 hours post-dose,^{31,34,35} and 2.5 hours post-dose²⁶ to 9-time sampling to construct 24 hours AUC.²⁷ However, all studies used standard methods for quantification of plasma level of the drug. The pharmacokinetics characteristics and associated treatment outcomes of each drug are presented below.

Rifampicin

Among the twelve studies, eleven studies assessed RMP pharmacokinetics of which eight reported treatment

Table 2 Characteristics of Included Studies

Author	Country	Mean (Median) Age of Study Participant	Study Design	Sample Size	Population Characteristics	Risk of Bias
Aarnoutse, (2017) ³⁰	Tanzania	33.5	Randomized Controlled Trial	150	15 HIV positive	Low
Burhan (2013) ³⁴	Indonesia	35	Prospective cohort	181	44 diabetic 19 HIV positive	Low
Pasipanodya (2013) ²⁵	South Africa	36	Prospective cohort	142	15 HIV positive 98 have prior tuberculosis	Low
Prahl (2014) ³¹	Denmark	42	Prospective cohort	32	2 HIV positive	Low
Requena-Méndez (2014) ³³	Peru	29	Prospective cohort	107	25 Diabetic 30 HIV positive	Low
Rockwood (2017) ²⁹	South Africa	33	Prospective cohort	100	65 HIV positive 4 diabetic	Low
Sekaggya-Wiltshire (2018)	Uganda	34	Prospective cohort	227	All HIV positive	Low
Svensson (2018) ²⁷	Tanzania and South Africa	34	Prospective cohort	97	2 patients HIV positive	Low
Vela'squez (2018) ³²	Peru	25	Randomized Controlled Trial	180 randomized to three arms 10, 15, and 20 mg/kg	2 patients HIV positive	Low
Gengiah (2014) ²⁶	South Africa	33	Prospective cohort	57	All are HIV positive	Low
Ramachandran (2017) ³⁵	India	38	Prospective cohort	1912	19 HIV positive 53 diabetic	Low
Ramachandran (2020) ³⁶	India	39.5	Prospective cohort	404	27 HIV infected 113 Diabetics	Low

outcomes.^{27,28,30–32,35,36} Ramachandran et al found that 91%, of the patients, had suboptimal concentrations of RMP (8 g/mL). This study evaluated factors influencing tuberculosis treatment outcomes in adult patients treated with thrice-weekly regimens. Lower RMP concentration was among the factors responsible for poor treatment outcome.³⁵ However, the study assessed multi-factors and the treatment was not according to current WHO recommendation. Similar authors recently have shown that low RMP concentrations were associated with poor outcomes.³⁶ Sekaggya-Wiltshire et al demonstrated that patients with both low RMP and INH Cmax have

a moderately increased risk of unfavorable treatment outcomes, including death, treatment failure, loss to follow-up, and default.²⁸ This study had a large sample size, but all study participants were HIV positive and there was no evidence on the effect of HIV on treatment outcome. Pasipanodya et al, compared treatment outcome using culture conversion at two months and long term outcome at two years for RMP peak concentration above and below 6.6 mg/L. Among the patients who have a peak concentration below 6.6mg/L, 19% have culture-positive at two months while only 1% have a culture-positive for the patient group who have a peak concentration above

Table 3 Pharmacokinetic Characteristics and Treatment Outcome

Author	Study Drug	Pharmacokinetics Bio-Analytical Methods	PK Parameter Considered	PK Sampling Time	Duration for Which the Study Participant Followed	Outcome Measured	The Proportion of Patient with Low PK	The Proportion of Patients with Poor Outcome	Conclusion on the Predictive of PK on Treatment Outcome at the End of Treatment
Aarmoutse, (2017) ³⁰	RMP	ultraperformance liquid chromatographic	Cmax	1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, and 24 hours	12 weeks	Time to culture conversion on different days	NA	72.2% from 600mg 62.9 from 900mg 73.8% from 1200mg have culture conversion on 84 days	Higher exposure to RMP was observed as the dose increase., but did not result in an improved bacteriological response in patients with pulmonary TB
Burhan (2013) ³⁴	INH, RMP, PZA	HPLC	Cmax	2 hours	8 weeks	Culture conversion at 8 weeks	INH= 88% RMP= 49% PZA=2%	11/155 have a positive culture at week 8	No association was found between drug concentration and 8 weeks of culture conversion
Pasipanodya (2013) ²⁵	INH, RMP, PZA	HPLC with UV detection for RMP, INH, and PZA; mass spectrometry for EMB	24-hours AUC I	0.5, 1, 1.5, 2, 2.5, 3, 4, 6, and 8 hours	For up to 2 years	Culture conversion at two months and long term outcome up to two years	PZA=69.7% RMP =70.7% INH =81%	11/142 did not convert culture at two months 25% of 142 patients had poor long-term outcomes	From CART analysis Low drug AUCs are predictive of clinical outcomes in tuberculosis patients PZA: AUC < 363 RMP: AUC <13 INH: AUC < 52
Prahl (2014) ³¹	INH, RMP, EMB, PZA	HPLC with tandem mass spectrometry	2 hours of concentration	2hours	For up to one year after completion of treatment	Failure at six months or a relapse of TB within 1 year after the end of treatment	INH= 71%, RMP=57.6% EMB= 46% PZA=10%	5/28 failure during one year follow up	Lower INH and RMP are observed in treatment failure

Requena-Méndez (2014) ³³	INH	HPLC with a triple-quadrupole TSQ Quantum Access mass spectrometer	C _{max} , and AUC(0–6h)	2 and 6 hours	6 months after completion of treatment	outcomes at the end of therapy and 6 months after the end of therapy	34% during the intensive phase and 33.3% during the continuation phase	4/41 (2 death, 1 relapse, and 1 prolonged treatment)	Unable to demonstrate a clear relationship between the C _{max} of INH and treatment outcome
Rockwood (2017) ²⁹	INH, RMP, PZA	HPLC with Tandem mass spectrometry	C _{max} AUC ₂₄ AUC ₀₋₂₄ /MIC, C _{max} /MIC	1, 2, 3, 4, 6, and 8 hours	2 months culture conversion	Culture conversion at two months	INH 43% C _{max} <3 mg/L and 6% <1.5 mg/L. RMP 80% C _{max} <8 mg/L and 17% <4 mg/L. PZA 53% C _{max} <35 mg/L and 1% <20 mg/L	13% overall treatment success without failure/relapse was observed	None of these C _{max} cutoff values for INH or RMP predicted 2-month culture conversion and/or failure/relapse but did predict failure/relapse for PZA
Selaggya-Wiltshire (2018) ²⁸	INH, RMP, PZA, EMB	HPLC	C _{max} and AUC	1, 2, and 4 hours	Up to 24 weeks after initiation of TB treatment	Cure, death, failure	INH = 83.7% RMP = 77.5% PZA = 2.64% EMB = 30.8%	Cure = 158 Death = 11 Failure = 8 Default = 2 Lost to follow up = 17	Patients with both low RMP and INH C _{max} have moderately increased risk of unfavorable treatment outcomes, including death, failure, loss to follow-up, and default
Svensson, (2018) ²⁷	RMP	ultraperformance HPLC	AUC ₂₄	0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours	Up to 26 weeks	time to stable sputum culture conversion (TSCC)	NA	NA	Increasing RMPampicin exposure to modestly shorter TSCC at week 8, TSCC increased from 39% to 55% with RMP AUC _{0-24h} increasing from 20 to 175 mg/L h

(Continued)

Table 3 (Continued).

Author	Study Drug	Pharmacokinetics Bio-Analytical Methods	PK Parameter Considered	PK Sampling Time	Duration for Which the Study Participant Followed	Outcome Measured	The Proportion of Patient with Low PK	The Proportion of Patients with Poor Outcome	Conclusion on the Predictive of PK on Treatment Outcome at the End of Treatment
Vela'squez (2018) ³²	RMP	NA	AUC ₂₄ /MIC	NA	Up to 12 months	Change in elimination rate of M. tuberculosis log10 colony-forming units- and culture conversion at 8 week and unfavorable outcome at 12 months	NA	At 12 month cure 10mg/kg =44/60, 15 mg/kg=46/60 And 20mg/kg =46/60	Increasing the dose enhanced rapid sputum sterilization
Gengiah (2014) ²⁶	RMP	Tandem HPLC mass spectrometry	Cmax	2.5 hours	Up to 6 months	Sputum at six months	All	8/55 sputum positive at two months 2/51 sputum positive at six months	No evidence, but in all patients Cmax is below the standard target
Ramachandran (2017) ³⁵	RMP, INH, and PZA	HPLC	2 hours plasma concentration	2hours	Up to end of therapy	Outcome at the end of treatment	RMP= 91%, INH= 16%, PZA = 17%	264 (14%) had an unfavorable outcome	Low RMP concentration is among the factors associated with treatment outcome
Ramachandran (2020) ³⁶	RMP, INH, and PZA	HPLC	2 hours of plasma concentration	2hours	Up to 2 years (24 months)	Outcome during the follow-up period	NA	77 (19%) patients have an unfavorable outcome	Low RMP and PZA concentrations were associated with poor outcomes

Abbreviations: NA, nonapplicable; RMP, rifampicin; INH, isoniazid; PZA, pyrazinamide; EMB, ethambutol; PK, pharmacokinetics; AUC, area under the curve; HPLC, high-performance liquid chromatographic.

6.6mg/L. A similar difference was also observed for a long outcome for patient group dichotomized to above and below 13 mg/L•h AUC, 12% and 33% poor outcome respectively.²⁵ Evidence on drug exposure and treatment outcome relationship was reported from two recent controlled clinical trials.^{30,32} In both studies increasing the dose of RMP increased drug exposure, however, improved faster culture conversion in the high exposure group was observed only in one study.³²

Svensson et al found an association between RMP concentrations and time to stable sputum culture conversion.²⁷ The proportion of patients with stable culture conversion on liquid medium at week 8 increased from 39% to 55%, with the RMP AUC increased from 20 to 175 mg/L•h. This study used only two dose levels, 10mg/kg and 35mg/kg, and the safety of 35mg/kg was not elucidated. Prah et al found that treatment failure was observed at lower INH and RMP concentrations.³¹ The remaining three studies have not shown any evidence on the association of RMP concentration and treatment outcome.^{26,29,34}

Isoniazid

The impact of plasma concentration of INH on treatment outcome was reported in eight studies. Requena-Méndez et al investigated the effects of dose, comorbidities, and food on INH pharmacokinetics in Peruvian tuberculosis patients. Although 34% of patients during the intensive phase and 33.3% during the continuation phase had lower INH concentration, no association between plasma concentration and treatment outcome was observed at the end of therapy.³³ Burhan et al evaluated the association of 2hour plasma concentration of INH and treatment outcome, however, no association was found.³⁴ Similarly, Rockwood et al reported no association between two months of culture conversion and pharmacokinetics. On the other hand, in Prah's study, patients with treatment failure had a significantly lower 2hour plasma concentration of INH than those who were cured.³¹ Pasipanodya et al, compared treatment outcomes using culture conversion at two months for INH peak concentration above and below 8.8 mg/L. Among the patients who have a peak concentration below 8.8mg/L, 13% have culture-positive at two months while no patients have a culture-positive for the patient group who have a peak concentration above 8.8mg/L. For the long-term treatment outcome assessment, the patient group who have AUC of INH above and below 52mg/L•h have 20% and 70% poor treatment outcomes

respectively.²⁵ Furthermore, Sekaggya-Wiltshire et al reported an association of low INH and RMP concentration with poor culture conversion.²⁸

Pyrazinamide

The clinical impact of PZA drug concentrations was assessed in seven studies. However, only three studies reported the association between PZA plasma concentration and treatment outcome.^{25,34,36} Pasipanodya et al reported an association of AUC less than 363 mg•h/L with poor long-term outcomes. Moreover, the highest predictor of 2-month sputum conversion among all clinical factors examined was PZA peak concentration. Burhan et al evaluated the relationship between the plasma concentration of INH, RMP, and PZA and treatment outcome. No association was found between RMP and INH plasma concentration and treatment outcome.³⁴ However, low pyrazinamide drug concentrations may be associated with a less favorable bacteriological response. Similarly, Rockwood et al found no association between Cmax of PZA and 2-month culture conversion culture but did predict failure or relapse.²⁹ Another recent study reported that a 1-μg/mL decrease in pyrazinamide concentrations was associated with recurrence.³⁶

Discussion

The WHO End TB Strategy has set an ambitious target to reduce TB deaths by 90% and to cut new cases by 80% between 2015 and 2030.² To achieve these ambitious targets requires various interventions. First, achieving the WHO end TB targets will necessitate better, and early detection of TB which could halt TB transmission and hasten the decline in TB incidence and mortality.^{37,38} Second, we need safer, shorter, and more efficacious treatment for all forms of TB. Third, a vaccine would be the ultimate solution if found to be highly effective, safe, able to prevent pre-exposure, infection as well as reactivation.^{39,40} Since the existing anti-tubercular regimens made before the current advance in pharmacokinetic-pharmacodynamic (PK-PD), we are lacking evidence of exposure-response relationships even in today's tuberculosis pharmacotherapy.⁴¹ Owing to this gap WHO developed a technical report on the PK and PD of drugs used for tuberculosis treatment.¹³ This review examined the literature published over the last ten years reporting pharmacokinetics in particular plasma concentration of first-line anti-tubercular drug association with treatment outcome.

The pharmacokinetics properties of first-line anti-TB drugs at which treatment success achieved have been published previously.¹⁶ The most common PK-PD measures used to describe anti-TB activities are the ratio of the C_{max} relative to the MIC and the ratio of the area under the concentration-time curve at the end of the dosing interval relative to the MIC (AUC_{0–24}/MIC).⁴ However, in several PK-PD studies, AUC_{0–24} or/and C_{max} of the first-line drug was used as a measure of exposure and response. Similarly, nine of the eleven studies reported in this review used either C_{max}, AUC, or both. Only one study described AUC₂₄/MIC³² and one another both AUC₂₄/MIC and C_{max}/MIC.²⁹ Besides, there is a variation in methods of determination of C_{max} and AUC. For instance, Prahl et al³¹ measured the C_{max} at 2 hours post-dose, but Gengiah et al measured it at 2 1/2 hours post-dose.²² For accurate prediction of AUC, although recent studies recommending a sparse sample of plasma are emerging,⁴² intensive blood sampling is essential. But estimation of AUC is also done using different approaches.

The prevalence of low concentration in all studies is high. Previous systematic review and meta-analysis have also shown a high prevalence of low plasma concentration.^{20–22} However, they failed to find a strong association between low concentration and treatment outcomes. The type of studies included, the reliability of the current therapeutic range and variation on the report of treatment outcome were listed as factors responsible for lack of association. Owing to this the present review assessed only prospective and controlled clinical trials.

Only eight of the eleven studies have found the association between drug concentration and treatment outcome for RMP.^{25,27,28,30,32,35,36} Aarnoutse et al observed faster culture conversion in the higher RMP exposure group;³⁰ Pasipanodya et al demonstrated AUCs of PZA, RMP and INH are predictive of clinical outcomes in tuberculosis patients;²⁵ Prahl et al observed lower INH and RMP concentration in treatment failure;³¹ Sekaggya-Wiltshire et al reported patients with both low RMP and INH C_{max} have delayed culture conversion;²⁸ Svensson et al²⁷ and Vela'squez et al³² have shown increasing RMP exposure to modestly shorter time to stable sputum culture conversion, and Ramachandran reported low RMP concentration as a predictive of treatment outcome.³⁵ Similarly, a recent report of Ramachandran et al identified lower peak concentration or AUC as a predictor of culture conversion at two months and long-term treatment outcome respectively.

From these findings, one could best describe that increase in exposure to RMP increases anti-mycobacterial effects. However, using the current reference range it is difficult to dichotomize tuberculosis patients into non-respondents and respondents to anti-mycobacterial drug therapy based on the concentration.

The prevalence of low drug concentration is high for INH and PZA. The previous meta-analysis has shown that pharmacokinetics variability of INH mediates acquired drug resistance.⁴³ Similarly, four studies reported the lower INH drug concentration associated with unfavorable treatment outcomes.^{25,28,31,33} Of the seven studies that assessed PZA concentration and treatment outcome Burhan et al and Pasipanodya et al identified low PZA concentration as a primary cause of unfavorable outcome.^{25,34} The results are consistent with the recent meta-analysis that needs attention in tuberculosis care.⁴⁴

From this qualitative review, it is clear that increased exposure to drugs can improve the treatment outcome. However, further studies are required to validate this observation because of the following reasons. First, some patients are respondents to low and very low concentrations of the drug.²⁶ Second, in most studies, the participants have a comorbid condition that could affect the outcome. Thus, to establish exposure-response relationship studies controlling confounding factors are important. Third, data are emerging on the effect of the strain of *Mycobacterium tuberculosis* variation on the clinical outcome [46] and variation on the critical concentration inhibiting wild-type *Mycobacterium tuberculosis* [47]. Therefore, to integrate the concentration of drug measurement into tuberculosis care and treatment better characterization of C_{max}, AUC, C_{max}/MIC, and/or AUC/MIC are needed.

Conclusion

This systematic review attempts to link drug exposure and treatment outcome. Although a limited number of prospective observational studies and controlled clinical trials are available for the review, RMP, PZA, and INH concentration have shown a link with treatment outcomes. An increase in exposure to RMP improved the outcome. A lower concentration of INH and PZA is observed in unfavorable treatment outcomes. On the other hand, a better outcome was observed in patients who have low exposure to these drugs. Further studies addressing the validity of the current reference range, plausible pharmacokinetics parameter, bacterial, and host factors are,

however, are needed to predict drug concentration and treatment outcome association.

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Disclosure

The authors report no conflicts of interest for this work.

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