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Effect of Bedaquiline and Delamanid Pharmacokinetics on Sputum Culture Conversion and Adverse Events in Drug-Resistant Tuberculosis

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Background: Pharmacokinetic studies of bedaquiline and delamanid in patients with pre-extensively drug-resistant tuberculosis (pre-XDR TB) will help in the optimization of these drugs for both culture conversion and adverse events.

Methods: A prospective cohort of 165 adult patients (56% male with mean [SD] age 29 [9.7] years) with pre-XDR TB was treated with bedaquiline, delamanid, clofazimine, and linezolid for 24 weeks at 5 sites in India. Bedaquiline was administered at 400 mg daily for 2 weeks followed by 200 mg thrice weekly for 22 weeks, whereas delamanid was administered at 100 mg twice daily. In 23 consenting participants at 8 and 16 weeks of treatment, blood was collected at 0, 2, 4, 5, 6, 8, 12, and 24 hours postdosing for an intense pharmacokinetic study. Pharmacokinetic parameters were correlated with sputum culture conversion and adverse events.

Results: The mean (SD) age and weight of patients were 30 (10) years and 54 kg, respectively. The median minimum concentration (C_{min}) and time–concentration curve (AUC) for bedaquiline, respectively, were 0.6 mcg/mL and 27 mcg/mL·h at week 8 and 0.8 mcg/mL and 36 mcg/mL·h at week 16, suggesting drug accumulation over time. The median C_{min} and AUC of delamanid, respectively, were 0.17 mcg/mL and 5.1 mcg/mL·h at week 8 and 0.20 mcg/mL and 7.5 mcg/mL·h at week 16. Delay in sputum conversion was observed in patients with drug concentrations lower than the targeted concentration. At weeks 8 and 16, 13 adverse events were observed. Adverse events were resolved through symptomatic treatment. Body mass index was found to be significantly associated with drug-exposure parameters.

Conclusions: Bedaquiline and delamanid when co-administered exhibit plasma drug levels within the targeted concentrations, showing an exposure–response relationship.

Key Words: plasma drug levels, therapeutic range, adverse events, sputum conversion

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INTRODUCTION

Studies on novel drug combinations for a shorter, all-oral regimen for the treatment of drug-resistant tuberculosis (TB) have demonstrated good treatment success rates.[1–3] With global estimates showing a 3% increase in drug-resistant TB in 2021, there will also be an increase in the use of newer drug regimens.[4] However, it is unclear whether the doses of new drugs like bedaquiline, delamanid, and pretomanid currently being used in these regimens are optimal because improper exposure to drugs can affect the treatment response, development of resistance, and toxicity.[5] A recent consensus-based report on clinical standards for dosing and management of TB drugs also highlights the need for tailoring optimal drug doses to ensure that TB treatment is safe and effective.[6]

Both the new drugs, bedaquiline and delamanid, have a high volume of distribution in the plasma, are highly bound to plasma proteins, and are hepatically

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metabolized.[7,8] Bioavailability of these drugs depend on several factors, including drug–food interaction, drug–herb interactions, and CYP3A4 interactions besides drug–drug interactions, all resulting in pharmacokinetic variability in clinical practice.[9] Understanding the pharmacokinetics of these drugs in combination will help us optimize the use of newer drugs without the fear of emerging resistance or toxicity in the background of malnutrition and extensive TB disease. Here, we report on the pharmacokinetic parameters of bedaquiline and delamanid in patients with multidrug resistant TB and additional drug resistance to fluoroquinolone and/or second-line injectable (pre-XDR TB) and its association with sputum culture conversion and adverse events in these patients.

STUDY METHOD

This was a substudy included in the BEAT-TB India study, which enrolled adults with pulmonary pre-XDR TB during the years 2019–2021 at 5 sites in India, namely Rajan Babu Institute of Pulmonary Medicine and Tuberculosis, New Delhi; National Institute for Research in Tuberculosis, Chennai; National Institute for Tuberculosis and Respiratory Diseases, New Delhi; Government Thiruvatteeswarar Hospital of Thoracic Medicine, Chennai; Group of TB Hospitals, Mumbai; and B.J. Medical College and Hospital, Ahmedabad. After pretreatment evaluations, patients were treated with a regimen containing bedaquiline, delamanid, linezolid, and clofazimine for 6–9 months.[2] Bedaquiline was given at 400 mg once daily for the first 2 weeks, then 200 mg thrice weekly for 6 months; delamanid was given at 100 mg twice daily; linezolid was given at 600 mg once daily; and clofazimine was given at 200 mg or 100 mg once daily, based on body weight. All drugs were administered under supervision after meals. Safety and toxicity were monitored throughout the treatment period. The study was approved by the institutional ethics committee of the National Institute for Research in Tuberculosis, Chennai and all the other participating sites. Written informed consent was obtained from all participants. The study was also registered with the Clinical Trials Registry of India (CTRI/2019/01/017310).

The selection of participants for the pharmacokinetic study was based on their apparent general condition, drug intake without any interruption, and absence of vomiting or diarrhea 5 days before the conduct of the pharmacokinetic study. Participants who had taken antituberculosis treatment without interruption during the previous week (minimum of 7 days) were included. An intense pharmacokinetic study was performed on days when the participant had a dose of bedaquiline. An evening dose of delamanid, on the day before the pharmacokeintic study, was administered under supervision. After obtaining informed written consent, blood samples for pharmacokinetic analysis were collected at 2 time points: at week 8 and week 16 of treatment. On the pharmacokinetics study day (week 8; day 57), 8 blood samples were collected over a period of 24 hours, that is, at 0 (predosing), 2, 4, 5, 6, 8, 12, and 24 hours postdosing. The same blood collection was repeated at week 16 (day 113).

Drug Quantification

Plasma bedaquiline and delamanid concentrations were quantified using a validated high-performance liquid chromatography (HPLC) assay.[10] Briefly, this method involved deproteinization and further extraction of bedaquiline and delamanid. Ascentis R Express C18 (15 cm × 4.6 mm ID, 2.7 mcg particle size) (Merck, Darmstadt, Germany) was used as the analytical column. The isocratic mobile phase consisted of 0.01 mol/L ammonium acetate buffer containing 0.25% acetic acid and 0.02% trifluroacetic acid and acetonitrile in the ratio of 20:80 (vol/vol). The solvents were degassed individually using a Millipore vacuum pump before preparing the mobile phase. The analytes were detected at a UV wavelength of 231 nm. The retention time for bedaquiline and delamanid were 5.4 and 2.5 minutes, respectively. The calibration curve was linear over a range of 0.01–10.0 mcg/mL for both bedaquiline and delamanid. The intraday and interday relative standard deviations for standards were below 10%. The accuracy of plasma bedaquiline and delamanid concentrations ranged from 93% to 102% of the nominal concentration. At the standard dose (200 mg 3 times weekly), we targeted/expected bedaquiline trough (C_{min}) and maximal concentration (C_{max}) to be 0.26–0.91 mg/L and 0.90–2.1 mg/L, respectively,[9,11] whereas the delamanid trough and maximal concentrations were 0.13–0.24 and 0.20–0.40 mg/L, respectively.[12]

Statistical Analysis

Based on the plasma concentrations of bedaquiline and delamanid at different time points, pharmacokinetic parameters including C_{max}, T_{max}, area under the time–concentration curve (AUC), half-life, and clearance were calculated. Data were entered in Excel (Microsoft, Redmond, WA), verified,

TABLE 1. Description of Participants in the Pharmacokinetic Study

Characteristics	Median (IQR) [n = 23]
Age (years)	28.0 (21.0–31.0)
Weight (kg)	52.0 (44.0–63.4)
Body mass index (kg/m^2)	20.6 (16.8–22.5)
	N (%)
Male sex	18 (78.3)
Number of smokers	4 (17.4)
Participants consuming alcohol	5 (21.7)
Participants with diabetes mellitus	4 (17.4)
Diagnosis	
Pre-XDR TB	21 (91.3)
XDR TB	2 (8.7)
Chest x-ray involvement	
>3 zones	8 (34.8)
Both lungs (bilateral)	13 (56.5)
Presence of cavity	15 (65.2)
Smear at baseline	
Scanty or 1+ bacilli	10 (44)
2+ or 3+ bacilli	13 (56)
MGIT culture positive at baseline	23 (100)

and presented as descriptive statistics using frequencies and percentages. Pharmacokinetic parameters were correlated with sputum culture conversion and adverse events. Adverse events as a result of the treatment regimen were assessed using Division of AIDS criteria and were attributed to a specific drug or drugs, based on the known toxicity profile of the drugs in the regimen.[13] A simple linear regression model was used to assess the association of covariates like age, sex, body mass index, weight, smoking, alcohol use, and diabetes status with the following exposure parameters: C_{min} and $AUC_{0–24h}$ of bedaquiline and delamanid. Statistical analysis was conducted using SPSS, version 23.0 (IBM, Armonk, NY).

RESULTS

A 24-hour intense pharmacokinetic study was conducted in 23 and 19 participants at week 8 and 16, respectively, for bedaquiline and delamanid. The mean and SD of age and weight were 30 (10.1) years and 54 (13.2) kg. None of the participants were co-infected with HIV, 4 had diabetes mellitus, and all were *Mtb* culture positive at baseline (Table 1).

Pharmacokinetic Parameters

Table 2 shows the pharmacokinetic parameters of bedaquiline and delamanid at weeks 8 and 16 in the study participants. The median $t_{1/2}$ was 16.0 and 16.5 for bedaquiline and it was 14.7 and 18.9 for delamanid at weeks 8 and 16, respectively. Similarly, the median C_{min} was 0.6 mcg/mL and 0.8 mcg/mL for bedaquiline and 0.17 mcg/mL and 0.20 mcg/mL for delamanid at weeks 8 and 16, respectively. At week 8, the median $AUC_{0–24h}$ for bedaquiline was 27.3 mcg/mL·h, whereas the median $AUC_{0–24h}$ for delamanid was 5.1 mcg/mL·h. The C_{min} of bedaquiline was higher than the average reported (0.36 mcg/mL) at both weeks 8 and 16, whereas the AUC was comparable with reported values. The median C_{min} and AUC (4.7 mcg/mL·h) of delamanid observed in this cohort were very similar to the expected values (Figs. 1A,B). With increasing duration of drug exposure, more participants showed higher plasma concentrations than the targeted/expected concentration of bedaquiline (>2 mcg/mL) unlike that for delamanid (Table 3).

Plasma Drug Levels and Sputum Culture Conversion

At the end of treatment, 21 participants showed a favorable outcome, defined as 2 consecutive negative sputum cultures taken at least 4 weeks apart during the last 3 months of treatment. Of the 21 patients with a favorable outcome, C_{max} value of bedaquiline was within the targeted concentrations in 5 participants and higher than the targeted concentration in 16 participants, whereas the delamanid levels were within the targeted concentration range in 9 participants and higher than the targeted concentrations in 12 participants. Of the 2 participants with unfavorable outcomes, one patient displayed a bedaquiline C_{max} higher than the targeted concentrations and delamanid C_{max} lower than the targeted concentrations; the other patient showed bedaquiline C_{max} lower than the targeted concentration and a delamanid C_{max} value within the targeted concentration. Figure 2 depicts the relationship between drug-exposure and treatment outcomes. Mean sputum culture conversion was observed at week 4 for patients with bedaquiline and delamanid C_{max} either within or higher than the targeted concentrations. One patient with bedaquiline C_{max} lower than the lowest targeted concentration had a delayed sputum culture conversion at week 12; after conversion, they remained culture negative until the end of treatment with a favorable response.

Plasma Drug Levels and Drug-Related Adverse Events

Fourteen participants did not have any bedaquiline or delamanid-related adverse reactions, while 9 participants reported 13 adverse events—2 participants showed increase in both liver and pancreatic enzyme levels, whereas one displayed QT corrected (QTc) prolongation at week 8, increase in liver enzyme levels at week 20, and increase in pancreatic enzyme levels at week 24 (Table 3).

Three participants showed QTc prolongation at week 6 (grade I), at week 8 (grade III), and at week 14 (grade II) post treatment. All 3 patients had C_{max} concentrations higher than

TABLE 2. Pharmacokinetic Parameters of Plasma Bedaquiline and Delamanid in the Study Cohort

Drug	Bedaquiline		Delamanid	
PK Parameters	**Week 8 [n = 23]**	**Week 16 [n = 19]**	**Week 8 [n = 23]**	**Week 16 [n = 19]**
C_{min} (mcg/mL)	0.6 (0.5–1.0)	0.8 (0.6–1.0)	0.2 (0.02–0.2)	0.2 (0.04–0.3)
C_{max} (mcg/mL)	2.1 (1.5–2.9)	2.4 (1.8–3.0)	0.3 (0.1–0.6)	0.4 (0.2–0.5)
T_{max} (mcg/mL)	5.0 (4.0–8.0)	5.0 (4.0–6.0)	5.0 (4.0–5.0)	5.0 (4.0–6.0)
$AUC_{0–24}$ (mcg/mL·h)	27.3 (21.4–39.5)	35.5 (29.2–38.8)	5.1 (1.3–7.5)	7.5 (2.7–9.1)
$AUC_{0-\infty}$ (mcg/mL·h)	49.6 (29.6–71.7)	65.2 (49.2–70.8)	10.3 (1.6–17.1)	13.2 (4.3–25.9)
Half-life (h)	16.0 (12.5–18.7)	16.5 (13.8–22.6)	14.7 (10.5–23.2)	18.9 (13.4–34.2)
Clearance (L)	4.7 (3.3–6.9)	3.1 (2.8–4.4)	19.4 (11.7–121.1)	15.2 (7.7–46.3)
Targeted Concentration	**Bedaquiline (1–2 mcg/mL), n (%)**		**Delamanid (0.10–0.36 mcg/mL), n (%)**	
Lower than targeted concentration	2 (9%)	0	4 (17%)	1 (5%)
Targeted concentration	9 (39%)	5 (26%)	8 (35%)	8 (42%)
Higher than targeted concentration	12 (52%)	14 (74%)	11 (48%)	10 (53%)

TABLE 3. Maximum Concentration of Bedaquiline and Delamanid at Weeks 8 and 16 With Respect to Adverse Events and Treatment Outcomes

Sex/ Age (y)	Bedaquiline		Delamanid		Adverse Events at 8th Week	Adverse Events at 16th Week	Outcome at the End of Rx
	C_{max}_8W (mcg/mL)	C_{max}_16W (mcg/mL)	C_{max}_8W (mcg/mL)	C_{max}_16W (mcg/mL)			
F/42	>2	>2	0.10–0.36	<0.10		Grade II QTc prolongation at 14th week	Cured
M/28	>2	>2	<0.10	0.10–0.36	Grade I QTc prolongation at 6th week	—	Death
M/21	>2	PK not done	<0.10	PK not done	—	—	Cured
M/33	1–2	>2	<0.10	0.10–0.36	—	—	Cured
M/29	>2	1–2	>0.36	>0.36	—	—	Cured
F/44	1–2	>2	>0.36	>0.36		Grade I elevated pancreatic enzymes at 12th week	Cured
M/29	1–2	>2	>0.36	>0.36		Grade I elevated pancreatic enzyme at 12th week & grade I elevation of liver enzyme at 20th week	Cured
M/19	>2	1–2	0.10–0.36	0.10–0.36	—	—	Cured
F/19	>2	>2	>0.36	>0.36	—	—	Cured
F/18	>2	>2	>0.36	>0.36	—	—	Cured
M/26	<1	PK not done	0.10–0.36	PK not done	—	—	Unfavourable outcome because of LZD toxicity
M/22	1–2	1–2	>0.36	>0.36	Grade I liver enzyme elevation at 4th week	—	Cured
M/27	1–2	1–2	>0.36	>0.36	—	—	Cured
M/28	<1	PK not done	0.10–0.36	PK not done	—	—	Cured
M/31	>2	>2	0.10–0.36	>0.36	—	—	Cured
M/55	>2	>2	>0.36	>0.36	Grade III QTc prolongation at 8th week	Grade I liver enzyme elevation at 20th week & grade I elevated pancreatic enzymes at 24th week	Cured
M/27	1–2	>2	>0.36	>0.36		Grade I liver enzyme elevation & grade II elevated pancreatic enzymes at 12th week	Cured
M/43	>2	>2	>0.36	0.10–0.36	—	—	Cured
M/46	1–2	PK not done	>0.36	PK not done	Grade II liver enzyme elevation at 6th week	—	Cured
M/20	1–2	>2	<0.10	0.10–0.36	—	—	Cured
M/30	>2	>2	0.10–0.36	0.10–0.36	—	—	Cured
F/28	1–2	1–2	0.10–0.36	0.10–0.36	—	—	Cured
M/18	>2	>2	0.10–0.36	0.10–0.36		Grade I liver enzyme elevation at 12th week	Cured

the highest target concentration of bedaquiline at weeks 8 and 16, while one displayed a C_{max} concentration higher than expected levels of both bedaquiline and delamanid. The QTc prolongation was resolved by the end of treatment without any drug interruptions. Six participants showed an increase in liver enzyme levels (5 with grade I and one with grade II). Of 6, 3 participants showed C_{max} concentrations higher than the highest targeted concentrations of both bedaquiline and delamanid, 2 participants showed C_{max} concentrations higher than the targeted concentration of delamanid, while one showed a C_{max} concentration higher than the targeted concentration of bedaquiline at weeks 8 and 16. Five participants had their adverse events resolved by the end of treatment without any drug interruption, while one participant with grade II increase in liver enzyme levels had treatment interrupted for 2 weeks, after which the anti-tuberculosis treatment was re-intiated, and the treatment was completed. Four patients had increased pancreatic enzyme levels (3 with grade I and one with grade II). All 4 participants had a C_{max} higher than the highest target concentrations for both bedaquiline and delamanid. Adverse events were resolved without treatment interruption in all 4 patients—2 by the end of treatment and 2 at 3 months post-treatment. None of the participants had adverse events that required hospitalization.

Of the 14 participants without any bedaquiline or delamanid-related adverse events, a C_{max} higher than the targeted C_{max} concentration of bedaquiline alone was observed in 5, that of delamanid alone was observed in one, and that of both bedaquiline and delamanid was observed in 5 patients.

A simple linear regression model revealed that for every unit increase in body mass index (BMI), the bedaquiline C_{min}

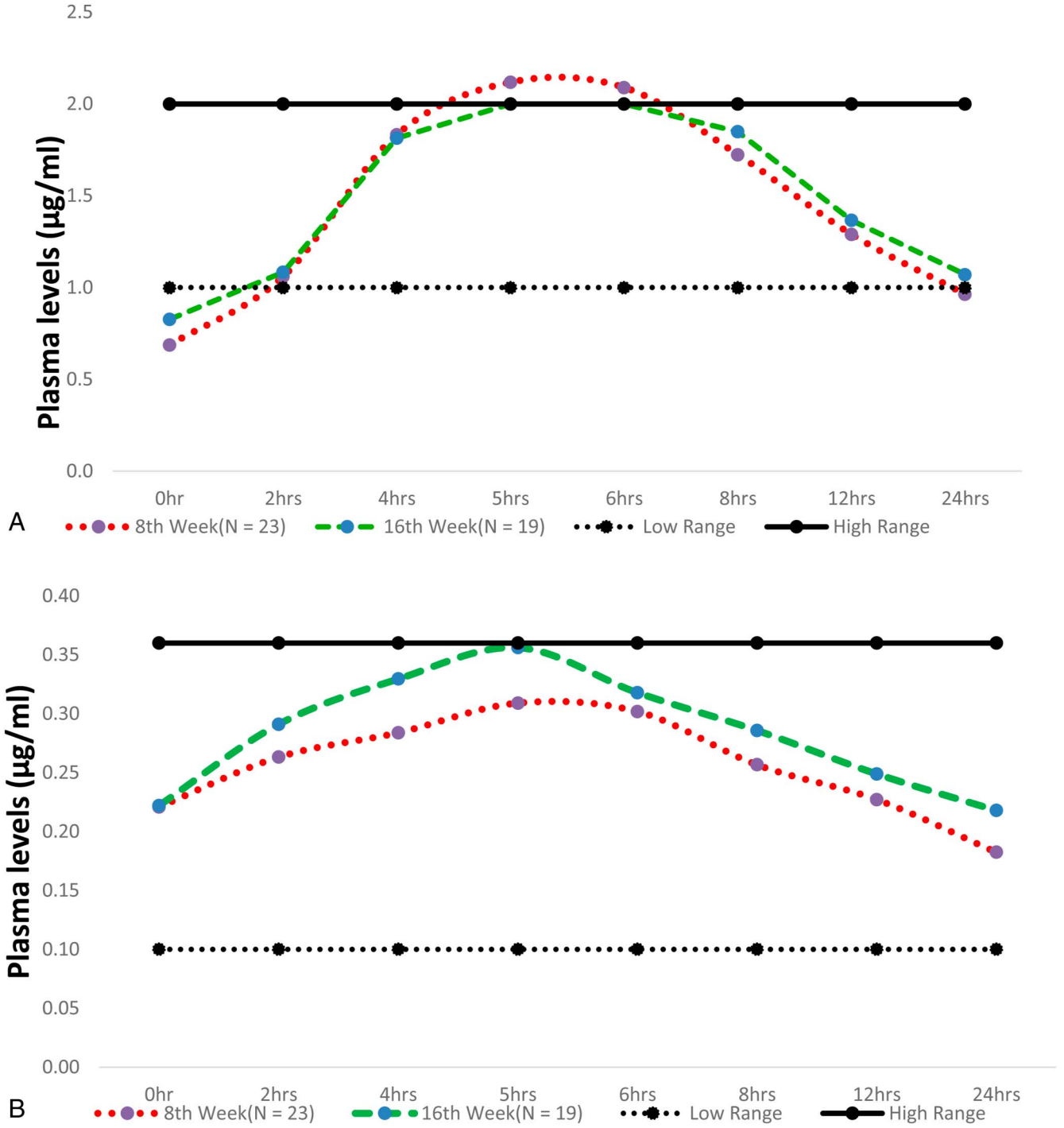

FIGURE 1. A, Mean plasma concentration of bedaquiline over a 24-hour PK period at weeks 8 and 16. B, Mean plasma concentration of delamanid over a 24-hour PK period at weeks 8 and 16.

dropped by 0.02 mg/L (P = 0.021) and AUC reduced by 0.78 mcg/mL (P = 0.02). Similarly, those with a body weight >50 kg had a lower AUC than those with a weight ≤50 kg (P = 0.03). Additionally, diabetes mellitus was associated with a higher C_{min} (P = 0.04) and AUC (P = 0.03) for bedaquiline, while this was not found for delamanid.

DISCUSSION

A combination regimen of bedaquiline and delamanid with other repurposed drugs has shown promising treatment outcomes with manageable adverse events in patients with pulmonary pre-XDR TB.[2] In this cohort, we simultaneously assessed the plasma levels of bedaquiline and delamanid in

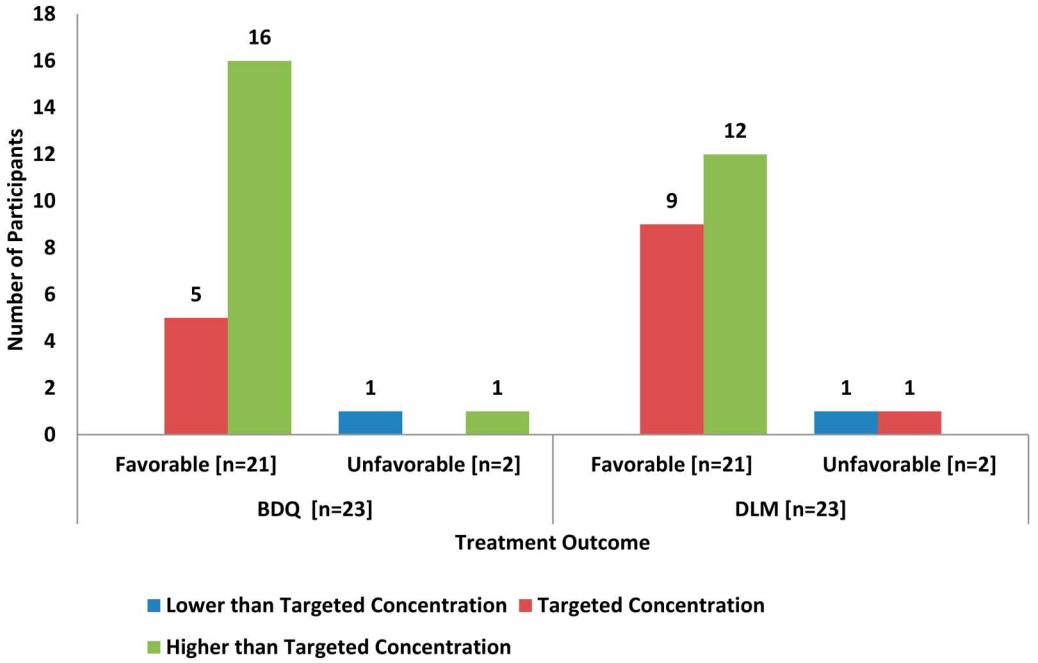

FIGURE 2. Column plot showing the drug exposure of bedaquiline and delamanid and treatment outcome in study participants.

plasma using HPLC and found no effect of bedaquiline–delamanid co-administration on their pharmacokinetics. We found accumulation of bedaquiline leading to higher plasma concentrations over time, unlike delamanid, with earlier culture conversion observed among those with a C_{max} higher than the targeted concentration of drugs. Our findings are in line with earlier studies that have shown an association between high bedaquiline concentrations and faster decline in bacterial load in patients with drug-resistant TB.[14,15] A multicentric study in China demonstrated that adequate exposure to bedaquiline, linezolid, and fluoroquinolones was associated with sputum culture conversion and favorable treatment responses in patients with drug-resistant tuberculosis.[16] This exposure–response relationship of bedaquiline paves the way for dose optimization and development of individualized treatment regimens for patients with difficult-to-treat drug-resistant TB.

The median clearance (CL) of bedaquiline was within the range reported in the literature (2.6–8.1 L/h) in patients with drug-resistant TB, although it decreased with a longer administration of the drug.[10,17] Similarly, the observed median C_{min} of bedaquiline was higher, noted both at week 8 (0.6 mcg/mL) and week 16 (0.8 mcg/mL) of treatment, than that in the study reported by Janssen et al where a mean C_{min} of 0.36 mcg/mL was observed at week 24 but was similar to results of other trials.[12] The AUC was comparable with reported values. The median C_{min} and AUC of delamanid observed in this cohort were very similar to the reported values.[18] With increasing duration of drug exposure, more participants showed bedaquiline C_{max} concentrations higher than the expected concentrations (>2 mcg/mL) unlike delamanid (Table 3). In this study, the pharmacokinetic assessments were carried out on 2 study days (weeks 8 and 16). The results showed that with the current dose of bedaquiline (loading dose of 400 mg OD daily for 14 days followed by 200 mg thrice weekly until the end of 24 weeks), concentrations higher than the targeted concentration were observed, and almost all the participants who had adverse events had a C_{max} concentration higher than the highest target concentration for at least one drug. An earlier study demonstrated a relationship between exposure of the bedaquiline M2 metabolite and prolongation of the QTcF interval, but no relationship could be identified between bedaquiline pharmacokinetics and transaminase levels.[19] One should also remember the potential for drug–drug interactions between bedaquiline and other co-administered drugs in the treatment regimen like clofazimine, which could increase the toxicity of bedaquiline.[20]

Similar to a cohort from Georgia, we too found that weight and BMI were inversely related to C_{min} and AUC of bedaquiline.[12] A mixed-effect pharmacokinetic modeling study reported that albumin concentrations, HIV co-infection, or bedaquiline coadministration did not have an effect on delamanid pharmacokinetics.[21]

This is the first study assessing the plasma levels of bedaquiline and delamanid in a cohort of patients with pre-XDR TB in India. One limitation of the study is its small sample size that limits any conclusions regarding an association between drug exposure and treatment outcomes. Additionally, exclusion of patients with a poor general condition may be considered as a selection bias for this study. In conclusion, we explored the association between pharmacokinetics of bedaquiline and delamanid with adverse events and sputum conversion. We infer that prolonged use of bedaquiline may result in plasma concentrations higher above the upper target concentration in a few patients, which may influence the QTcF interval. However, ACTG A5343 showed

that combining bedaquiline and delamanid had a modest, and no more than additive, effect on the QTc interval, providing evidence for the combined use of bedaquiline and delamanid in patients with drug-resistant TB and normal pretreatment QTcF intervals.[22] Weight and BMI were found to be associated with exposure parameters of bedaquiline (C_{min} and AUC), suggesting the need for weight-based dosing of bedaquiline. Given the expertise and infrastructure required to perform therapeutic drug monitoring and interpretation of the results, it probably cannot be widely carried out; however, it is recommended in cases of a lack of treatment response, intolerability, toxicity, and in cases of suspected drug–drug interactions.

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