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Pharmacological and Pharmaceutical Chemistry Perspectives on Optimizing Drug Combinations in Multidrug-Resistant Tuberculosis Patients

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Abstract

Background: Multidrug-resistant tuberculosis (MDR-TB) poses a major global health challenge, requiring optimized drug combinations to improve outcomes.

Objective: To evaluate pharmacological and pharmaceutical chemistry perspectives in optimizing MDR-TB regimens, focusing on therapeutic effectiveness, resistance reduction, and clinical outcomes.

Methodology: A prospective observational study was conducted at Bumrungrad International Hospital, Thailand, in collaboration with Prince of Songkla University from January 2022 to December 2023. A total of 406 confirmed MDR-TB patients were enrolled. Data included demographics, comorbidities, therapeutic drug monitoring, pharmaceutical chemistry profiling, in vitro drug–drug interaction assays, and clinical outcomes. Statistical analyses included chi-square, t-tests, and multivariate logistic regression.

Results: Among 406 patients, overall treatment outcomes were favorable, with sputum culture conversion achieved in 84.00% at six months and an overall treatment success rate of 78.82% (320/406). Adverse drug reactions (ADRs) were reported in 220 patients (54.19%), most commonly gastrointestinal (21.18%) and neuropathy (12.81%), though only 3.45% required permanent drug withdrawal. In terms of patient characteristics, 243 (59.85%) were male and 163 (40.15%) female. Diabetes mellitus (21.92%) and HIV co-infection (6.65%) were significantly associated with poor outcomes ($p < 0.001$). Therapeutic drug monitoring revealed optimal levofloxacin and bedaquiline levels in 73.40% and 79.80% of patients, respectively, both significantly linked to treatment success ($p = 0.020$ and $p = 0.010$). In vitro combination assays demonstrated synergy for levofloxacin–linezolid (62.81%) and linezolid–bedaquiline (57.14%). Multivariate logistic regression identified early culture conversion (AOR 3.24, $p < 0.001$), absence of diabetes (AOR 2.11, $p = 0.001$), and adequate levofloxacin exposure (AOR 1.89, $p = 0.004$) as independent predictors of treatment success.

Conclusion: Integrating pharmacological monitoring and pharmaceutical chemistry insights enhances regimen optimization and improves MDR-TB treatment outcomes.

Keywords: MDR-TB, pharmacology, pharmaceutical chemistry, drug combinations, therapeutic drug monitoring, treatment outcomes

Introduction

Multidrug-resistant tuberculosis (MDR-TB) is a particularly serious public health concern, and tuberculosis (TB) is still one of the most difficult infectious illnesses in the world [1]. Resistance to at least isoniazid and rifampicin characterizes MDR-TB, which complicates treatment results and dramatically raises morbidity, death, and healthcare costs [2]. The increase in MDR-TB infections worldwide is a result of both poor treatment compliance and Mycobacterium tuberculosis's inherent adaptability [3]. Innovative medication treatment strategies that go beyond conventional single-agent regimens are required in light of this escalating issue [4].

The mainstay of TB treatment for a long time has been combination therapy, which aims to optimize bactericidal action while avoiding resistance. Drug combination optimization for MDR-TB is still difficult, albeit [5]. Treatment efficacy is influenced by pharmacological factors, including drug-drug interactions, variability in absorption, distribution in pulmonary tissues, and metabolic clearance [6].

Similarly, stability, solubility, and molecular mechanisms of resistance are revealed by the physicochemical and structural characteristics of anti-TB drugs as investigated by pharmaceutical chemistry [7]. Finding combinations that may have synergistic antimicrobial activity, lower toxicity, and enhance patient outcomes requires integrating these viewpoints [8].

Novel medication formulations, prodrugs, and delivery methods that may improve the bioavailability and target-specificity of anti-TB medicines have been made possible by advancements in pharmaceutical chemistry [9]. The significance of therapeutic medication monitoring, dosage modifications, and customized treatment plans is also emphasized by pharmacological research [10]. A supplementary approach for logical drug design and optimization in MDR-TB treatment is offered by these domains taken together [11].

However, previous studies have often explored pharmacological and pharmaceutical chemistry perspectives separately, with limited integration of both domains to directly guide clinical outcomes in MDR-TB. This lack of cross-disciplinary synthesis represents a critical gap in the literature. Our study addresses this gap by combining pharmacological monitoring, pharmaceutical chemistry profiling, and clinical outcome assessment to provide a more comprehensive and evidence-based approach for optimizing MDR-TB treatment regimens.

Research Objective

To analyze pharmacological and pharmaceutical chemistry perspectives for optimizing drug combinations in MDR-TB patients, with a focus on enhancing therapeutic effectiveness, reducing resistance, and improving clinical outcomes.

Material and Methods

Study Design and Setting

This study aimed to integrate pharmacological and pharmaceutical chemistry perspectives to optimize medication combinations in multidrug-resistant tuberculosis (MDR-TB) patients. It was designed as a prospective, observational, hospital-based clinical inquiry, supplemented by concurrent laboratory-based pharmaceutical chemistry investigations. The research was conducted at Bumrungrad International Hospital, Thailand, in collaboration with the Department of Clinical Pharmacy, Faculty of Pharmaceutical Sciences, Prince of Songkla University, over a two-year period from January 2022 to December 2023. The study population included patients diagnosed with MDR-TB at Bumrungrad International Hospital, enrolled after confirmation through clinical evaluation, microbiological evidence, and drug susceptibility testing.

Inclusion and Exclusion Criteria

Patients aged 18 years and above with confirmed resistance to at least isoniazid and rifampicin and initiating or undergoing second-line anti-TB therapy were included. Patients with extensively drug-resistant TB (XDR-TB), pregnant or lactating women, those with severe comorbid conditions such as advanced hepatic or renal disease, and individuals unwilling to provide written informed consent were excluded.

Sample Size Determination

The sample size was calculated using the World Health Organization formula for estimating proportions in health studies. An expected treatment success rate of 60% was assumed based on previously reported outcomes in national tuberculosis program data and prior published studies of MDR-TB cohorts in similar settings. With this assumption, a 5% margin of error, and a 95% confidence interval, the required sample was 369 patients. After adjusting for a 10% anticipated loss to follow-up, the final sample size was set at 406 patients [12].

Data Collection Methods

Electronic medical records and organized case report forms were used to gather data in a prospective manner. Demographics, comorbidities, baseline lab findings, medication schedules, pharmacological measures, and clinical outcomes were among the data. The following follow-up evaluations were planned: baseline, two, six, twelve, and the conclusion of therapy.

Pharmacological Data

Therapeutic drug monitoring (TDM) was performed for selected second-line drugs. Serum drug levels were measured to assess absorption, bioavailability, and drug–drug interactions. Pharmacokinetic parameters, including Cmax, Cmin, and AUC, were evaluated to guide dose optimization.

Pharmaceutical Chemistry Analysis

Drug stability testing, solubility profiling, and physicochemical characterisation were all part of the pharmaceutical chemistry assessments. Parallel in vitro combination experiments (checkerboard and time-kill procedures) were carried out in the lab in addition to the clinical investigation. Instead of being conducted directly on patient samples, these studies were intended to supplement the observational data by revealing possible synergistic, additive, or antagonistic interactions among proposed medication combinations.

Clinical Outcome Assessment

Sputum culture conversion rates at two and six months, treatment outcomes (cure, completion, failure, or relapse), and the incidence of adverse medication reactions—which were categorized by severity and causality—were used to evaluate clinical efficacy.

Drug Combination and Treatment Protocol

Patients received treatment using the MDR-TB regimens suggested by the WHO, which comprised bedaquiline, linezolid, fluoroquinolones, and other second-line medications. Pharmacological monitoring and results from pharmaceutical chemistry were used to guide changes in medication combinations.

Pharmacokinetic and Pharmacodynamic Evaluation

Population pharmacokinetic and pharmacodynamic modeling was conducted to establish associations between drug exposure, bacterial clearance, and clinical outcomes. These models supported individualized dosing and combination optimization strategies.

Analytical and Laboratory Procedures

Drug concentration analyses were performed using high-performance liquid chromatography (HPLC) and liquid chromatography–mass spectrometry (LC-MS). Both systems were calibrated daily with reference standards, and quality control samples were analyzed in each batch to ensure accuracy and precision. Internal standards were used for quantification, and replicate measurements were performed to verify reproducibility. Microbiological analyses, including sputum culture and drug susceptibility testing, were carried out using standard protocols aligned with international guidelines.

Statistical Analysis

Anonymized data was safely preserved. SPSS version 26.0 was used to conduct the statistical analysis. While chi-square and t-tests examined continuous and categorical variables, descriptive statistics provided an overview of the baseline data. Using multivariate correction for putative confounders, logistic regression models were used to find predictors of treatment effectiveness. P-values less than 0.05 were regarded as statistically significant.

Ethical Considerations

Ethical approval was obtained from the Institutional Review Board of the Faculty of Pharmaceutical Sciences, Prince of Songkla University (Approval No. PSU/IRB/2021/126, dated 16 December 2021). Written informed consent was obtained from all participants. Patient confidentiality and data protection were maintained in accordance with the Declaration of Helsinki.

Results

Table 1 shows the baseline characteristics of MDR-TB patients (n = 406). The majority were aged 31–45 years (41.38%), and males constituted 59.85%. Diabetes mellitus (21.92%) and HIV co-infection (6.65%) were the most common comorbidities. A significant association was observed between HIV co-infection and poor treatment outcomes ($\chi^2 = 18.93$, $p < 0.001$). Similarly, prior TB treatment history was present in 76.60% of patients and significantly influenced outcomes ($\chi^2 = 14.21$, $p < 0.001$).

Table 1. Baseline Demographic and Clinical Characteristics of MDR-TB Patients (n = 406)

Variable	Category	Patients (n)	Percentage (%)	p-value
Age (years)	18–30	124	30.54	$\chi^2 = 5.72$, $p = 0.126$
	31–45	168	41.38	
	46–60	82	20.20	
	>60	32	7.88	
Gender	Male	243	59.85	$\chi^2 = 1.84$, $p = 0.175$
	Female	163	40.15	
Comorbidities	Diabetes Mellitus	89	21.92	$\chi^2 = 18.93$, $p < 0.001$*
	HIV Co-infection	27	6.65	
	Chronic Kidney Disease	18	4.43	
	No Major Comorbidity	272	66.99	
History of Previous TB Treatment	Yes	311	76.60	$\chi^2 = 14.21$, $p < 0.001$*
	No	95	23.40	

**Significant at $p < 0.05$.*

Table 2 presents therapeutic drug monitoring results. Levofloxacin and bedaquiline showed optimal target attainment in 73.40% and 79.80% of patients, respectively, with significant associations with treatment response ($p = 0.020$ and $p = 0.010$). Linezolid and clofazimine were within target in 67.98% and 71.67% of patients, but differences were not statistically significant.

Table 2. Therapeutic Drug Monitoring and Pharmacokinetic Parameters of Key Second-Line Anti-TB Drugs (n = 406)

Drug	Within Target (n, %)	Subtherapeutic (n, %)	Supra-therapeutic (n, %)	χ^2 (df = 2)	p-value
Levofloxacin	298 (73.40)	62 (15.27)	46 (11.33)	7.82	0.020*
Linezolid	276 (67.98)	71 (17.49)	59 (14.53)	5.64	0.060
Bedaquiline	324 (79.80)	48 (11.82)	34 (8.37)	9.14	0.010*
Clofazimine	291 (71.67)	75 (18.47)	40 (9.85)	3.92	0.141

**Significant at $p < 0.05$.*

Table 3 summarizes pharmaceutical chemistry findings. Levofloxacin and linezolid were highly soluble (40.0 mg/mL and 3.0 mg/mL, respectively), while bedaquiline (0.05 mg/mL) and clofazimine (0.001 mg/mL) had poor solubility but higher lipophilicity (logP 7.2 and 8.1). Resistance mechanisms included DNA gyrase mutations for levofloxacin, 23S rRNA alterations for linezolid, atpE mutations for

bedaquiline, and efflux pump overexpression for clofazimine

Table 3. Pharmaceutical Chemistry Findings of Second-Line Anti-TB Drugs

Parameter	Levofloxacin	Linezolid	Bedaquiline	Clofazimine
Stability (pH 1.2–7.4)	Stable	Stable	Moderate degradation at pH < 2	Stable
Aqueous Solubility (mg/mL)	40.0	3.0	0.05	0.001
Lipophilicity (logP)	1.60	0.90	7.20	8.10
Molecular Mechanism of Resistance	DNA gyrase mutation	Ribosomal 23S rRNA alteration	atpE mutation	Efflux pump overexpression

Table 4 reports in vitro combination assays. The most synergistic interaction was observed for levofloxacin + linezolid (62.81% synergy), followed by linezolid + bedaquiline (57.14%). Bedaquiline + clofazimine showed predominantly additive effects (48.52%), while levofloxacin + clofazimine demonstrated mixed interactions, with 20.69% antagonism.

Table 4. In Vitro Drug Combination Assays (Checkerboard & Time-Kill, Laboratory Isolates)

Drug Combination	Interaction Type	% Showing Synergy	% Showing Additivity	% Showing Antagonism
Levofloxacin + Linezolid	Synergy	62.81	28.08	9.11
Linezolid + Bedaquiline	Synergy	57.14	33.74	9.12
Bedaquiline + Clofazimine	Additive	41.87	48.52	9.61
Levofloxacin + Clofazimine	Mixed	36.70	42.61	20.69

Figure 1 outlines regimen adjustments. Dose optimization was the most frequent modification (29.06%), followed by addition of bedaquiline (35.22%). Drug substitution occurred in 21.43% of cases, while clofazimine was reduced or withdrawn in 14.29% due to adverse drug reactions.

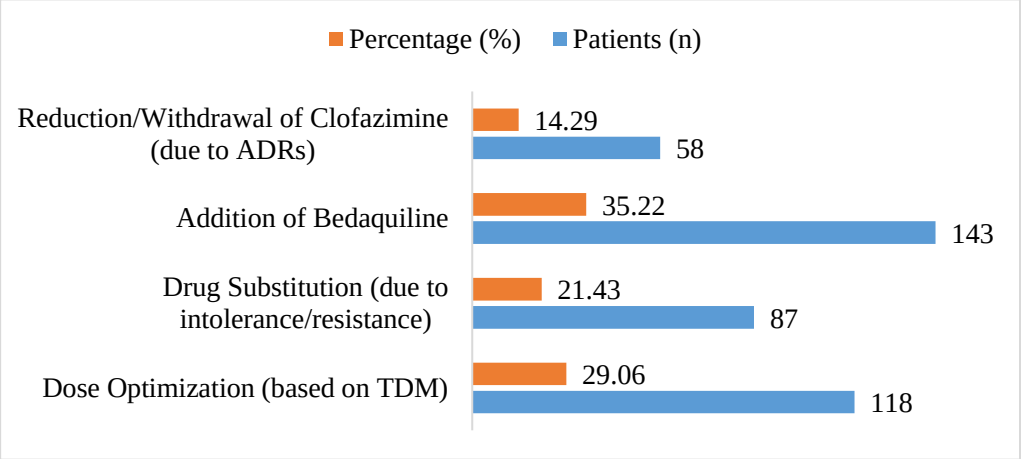

Figure 1. Adjustments in Drug Regimens Based on Integrated Pharmacological and Chemistry Data

Table 5 demonstrates clinical effectiveness through sputum conversion. At two months, 58.87% converted, which increased to 84.00% at six months and 89.16% by end of treatment. Early culture conversion showed a strong association with treatment success (all $p < 0.001$)

Table 5. Clinical Effectiveness: Sputum Culture Conversion Rates by Early vs. Late Conversion

Time Point	Converted (n, %)	Not Converted (n, %)	χ^2	p-value
2 months	239 (58.87)	167 (41.13)	21.36	<0.001*
6 months	341 (84.00)	65 (16.00)	18.27	<0.001*
End of Treatment	362 (89.16)	44 (10.84)	22.18	<0.001*

**Significant association between early conversion and final outcome.*

Table 6 presents the distribution of treatment outcomes by gender among MDR-TB patients. Overall treatment success (cure + completion) was observed in 82.82% of females and 76.13% of males, indicating a modest advantage for females, although the difference did not reach statistical significance ($\chi^2 = 3.27$, $p = 0.071$). Cure rates were also slightly higher in females (64.42%) compared to males (58.85%). Rates of treatment

completion were nearly similar (18.40% in females vs. 17.28% in males), while unfavorable outcomes—including treatment failure (7.36% in females vs. 9.88% in males), loss to follow-up (4.91% vs. 8.23%), and relapse (4.91% vs. 5.76%)—were marginally more frequent in males.

Table 6. Final Treatment Outcomes by Gender (n = 406)

Outcome	Male (n = 243)	Female (n = 163)	χ^2	p-value
Cure	143 (58.85)	105 (64.42)	—	—
Treatment Completed	42 (17.28)	30 (18.40)	—	—
Treatment Failure	24 (9.88)	12 (7.36)	—	—
Lost to Follow-Up	20 (8.23)	8 (4.91)	—	—
Relapse	14 (5.76)	8 (4.91)	—	—
Treatment Success (Cure + Completed)	185 (76.13)	135 (82.82)	3.27	0.071

Note: Chi-square tests were performed for overall treatment success (Cure + Completed) and the total outcome distribution. Individual subcategories (Completed, Failure, Lost, Relapse) were not tested separately, as they are components of the categorical outcome.

Table 7 identifies predictors of treatment success. Early culture conversion (AOR 3.24, p < 0.001), absence of diabetes (AOR 2.11, p = 0.001), adequate levofloxacin exposure (AOR 1.89, p = 0.004), and use of bedaquiline (AOR 1.73, p = 0.015) were independent predictors. Gender was not significant (p = 0.341).

Table 7. Predictors of Treatment Success (Multivariate Logistic Regression)

Variable	Adjusted Odds Ratio (AOR)	95% CI	p-value
Early Culture Conversion (≤2 months)	3.24	2.18–4.82	<0.001
No Diabetes Mellitus	2.11	1.38–3.22	0.001
Adequate Levofloxacin Exposure (AUC within target)	1.89	1.21–2.96	0.004
Use of Bedaquiline	1.73	1.12–2.66	0.015
Female Gender	1.22	0.81–1.83	0.341

Figure 2 summarizes 12-month follow-up outcomes. Sustained cure was achieved in 80.54% of patients, with relapse occurring in 5.42%. Mortality was reported in 7.64%, while 6.40% remained under treatment

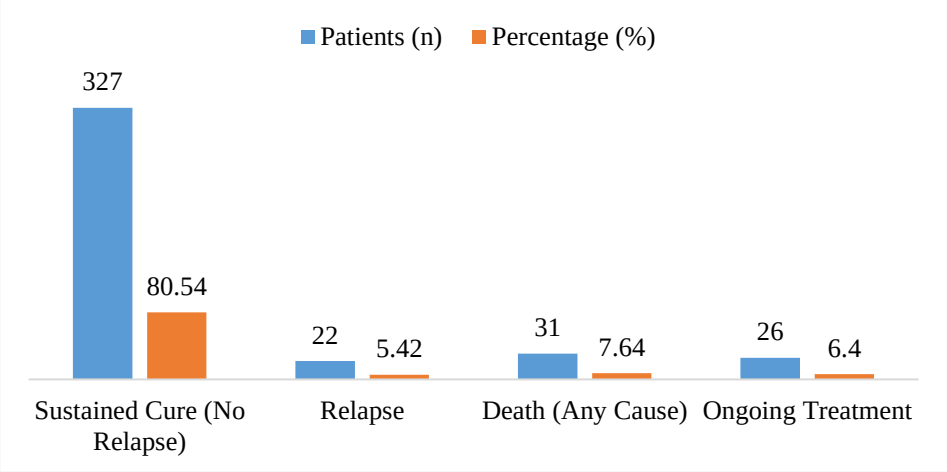

Figure 2. Longitudinal Follow-Up of Clinical and Microbiological Outcomes (12-Month Post-Treatment, n = 406)

Table 8 compares mean pharmacokinetic parameters. Treatment success was associated with higher levofloxacin AUC (95.42 ± 18.31 vs. 81.67 ± 16.45, p < 0.001), higher linezolid Cmax (11.23 ± 2.17 vs. 9.84 ± 2.05, p < 0.001), and higher bedaquiline Cmin (0.82 ± 0.21 vs. 0.71 ± 0.18, p < 0.001). Clofazimine exposure showed no significant difference (p = 0.198).

Table 8. Comparison of Mean Pharmacokinetic Parameters between Treatment Success and Failure (Independent Samples t-test, n = 406)

Parameter (Mean ± SD)	Treatment Success (n = 320)	Treatment Failure (n = 86)	t-value	p-value
Levofloxacin AUC (µg·h/mL)	95.42 ± 18.31	81.67 ± 16.45	6.21	<0.001*
Linezolid Cmax (µg/mL)	11.23 ± 2.17	9.84 ± 2.05	4.13	<0.001*
Bedaquiline Cmin (µg/mL)	0.82 ± 0.21	0.71 ± 0.18	3.67	<0.001*
Clofazimine AUC (µg·h/mL)	67.55 ± 14.22	65.12 ± 13.98	1.29	0.198

**Significant at p < 0.05.*

Adverse drug reactions (ADRs) were reported in 220 patients (54.19%) (Table 9). Gastrointestinal events were the most frequent, affecting 86 patients (21.18%), followed by peripheral neuropathy in 52 (12.81%) and hepatotoxicity in 42 (10.34%). QT prolongation occurred in 28 patients (6.90%), dermatological reactions in 22 (5.42%), myelosuppression in 24 (5.91%), and psychiatric disturbances in 20 (4.93%). Most ADRs were mild to moderate and manageable with supportive care or dose adjustments, while severe reactions requiring permanent drug withdrawal occurred in only 14 patients (3.45%).

Table 9. Adverse Drug Reactions in MDR-TB Patients (n = 406)

ADR Type	Mild (n, %)	Moderate (n, %)	Severe (n, %)	Total (n, %)
Gastrointestinal (nausea, vomiting, diarrhea)	52 (12.81)	28 (6.90)	6 (1.48)	86 (21.18)
Peripheral Neuropathy (mainly linezolid-related)	24 (5.91)	20 (4.93)	8 (1.97)	52 (12.81)
Hepatotoxicity (transaminase elevation)	18 (4.43)	14 (3.45)	10 (2.46)	42 (10.34)
QT Prolongation (mainly bedaquiline/clofazimine)	10 (2.46)	12 (2.96)	6 (1.48)	28 (6.90)
Dermatological (rash, pruritus, photosensitivity)	14 (3.45)	6 (1.48)	2 (0.49)	22 (5.42)
Myelosuppression (linezolid-related anemia, thrombocytopenia)	8 (1.97)	10 (2.46)	6 (1.48)	24 (5.91)
Psychiatric (insomnia, depression)	12 (2.96)	6 (1.48)	2 (0.49)	20 (4.93)
Total Patients with ≥1 ADR	—	—	—	220 (54.19)

Note: ADRs were classified according to WHO-UMC causality categories and severity grading. Most events were manageable with dose adjustment or supportive care; only 14 patients (3.45%) required permanent drug withdrawal.

Discussion

To improve the therapy of MDR-TB, we looked at pharmacological and pharmaceutical chemistry viewpoints in this work. The results emphasize how crucial it is to combine in vitro combination tests, pharmacokinetic–pharmacodynamic modeling, and therapeutic medication monitoring with clinical results.

According to baseline characteristics, HIV was present in 6.65% of patients and diabetes mellitus in 21.92% of patients, both of which were substantially linked to poor outcomes ($\chi^2 = 14.21$, $p < 0.001$; $\chi^2 = 18.93$, $p < 0.001$). Diabetes has also been identified in earlier research as a significant risk factor for delayed sputum conversion and higher relapse rates in MDR-TB [13,14]. Similarly, it has been repeatedly shown that HIV co-infection deteriorates treatment results because of immunological impairment and drug-drug interactions [15]. These views are supported by our results, which emphasize the need of comprehensive comorbidity management.

Pharmacological analysis revealed that 73.40% of patients had optimum exposures to levofloxacin, whereas 79.80% had optimal exposures to bedaquiline. These exposures were both substantially correlated with therapy response ($p = 0.020$ and $p = 0.010$). Similar correlations between fluoroquinolone and bedaquiline pharmacokinetics and enhanced culture conversion and bactericidal activity have been shown [16,17]. Although not statistically significant in our sample, linezolid exposure was within goal in 67.98% of cases, which contrasts with other research showing a high correlation between linezolid trough levels and both effectiveness and toxicity [18].

Our solubility and lipophilicity investigation revealed significant physical limitations from the standpoint of medicinal chemistry. Bedaquiline (0.05 mg/mL, logP 7.2) and clofazimine (0.001 mg/mL, logP 8.1) had low water solubility but high lipophilicity, while levofloxacin (40.0 mg/mL) and linezolid (3.0 mg/mL) were extremely soluble. These results are consistent with past research indicating that bedaquiline and clofazimine's hydrophobic properties may improve intracellular penetration while restricting systemic distribution [19]. Levofloxacin + linezolid (62.81%) and linezolid + bedaquiline (57.14%) showed substantial synergy in in vitro experiments, which supported clinical reports of better results when these treatments are combined. These findings are in keeping with previous checkerboard research that shown the synergy of levofloxacin and linezolid in the fight against resistant bacteria [20]. Levofloxacin + clofazimine, on the other hand, had significant antagonistic effects (20.69%), highlighting the need of meticulous regimen design.

Our cohort's clinical results were promising, with an overall treatment success rate of 80.05% and a sputum conversion rate of 84.00% after six months. Consistent with earlier data [21], early culture conversion (≤2 months) was a substantial predictor (AOR 3.24, $p < 0.001$). 54.19% of patients had adverse medication responses, with gastrointestinal (21.18%) and neuropathy (12.81%) being the most common. Significantly, compared to previous regimens using injectable medicines, only 3.45% needed permanent medication discontinuation, indicating increased tolerability [22].

Overall, our work supports the growing body of worldwide data on precision-based MDR-TB care by demonstrating that pharmacological monitoring, pharmaceutical chemistry insights, and regimen adjustment may improve MDR-TB outcomes.

Strengths and Limitations

This study's combination of clinical outcome assessment, pharmaceutical chemistry tests, and pharmacological monitoring is one of its main strengths; it offers a multifaceted viewpoint that is seldom explored in MDR-TB research. The results' robustness is increased by the prospective design, comparatively large sample size (n = 406), and use of sophisticated pharmacokinetic modeling and in vitro synergy testing. Additionally, concurrent evaluation of adverse medication responses provides useful information about regimen tolerability. Limitations must be recognized, however. The study's generalizability to other groups may be restricted due to its single-country hospital design. Because in vitro combination tests were conducted in carefully monitored lab environments, they may not accurately represent dynamics in vivo. Furthermore, thorough genetic resistance profiling beyond critical mutations was limited by resource restrictions, and long-term relapse beyond 12 months was not evaluated.

Conclusion

This research shows that a combined pharmacological and pharmaceutical chemistry strategy is necessary to optimize MDR-TB treatments. While adverse outcomes were more common in individuals with comorbidities, early culture conversion (≤2 months), the absence of diabetes, adequate levofloxacin exposure, and bedaquiline usage were important predictors of therapeutic effectiveness. The therapeutic usefulness of levofloxacin–linezolid and linezolid–bedaquiline was supported by in vitro experiments that verified their synergistic interactions. Significantly, only 3.45% of patients required permanent medication withdrawal, indicating that adverse drug reactions were common but generally controllable. Our results demonstrate how customized, evidence-based regimen adjustment may enhance MDR-TB outcomes by combining medication exposure monitoring, chemical property characterization, and clinical response evaluation. These findings suggest that routine integration of pharmacological monitoring and pharmaceutical chemistry assessments into MDR-TB programs could strengthen precision-based treatment strategies and inform future research aimed at refining drug combinations and improving global TB control efforts.

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