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Original Research Article

Evaluation of adverse drug reactions in patients receiving second-line therapy for multidrug-resistant tuberculosis

Venkat Sri Rangan P. B.[1], Sabia Sikander[2], Mohammed R. Darga[3], Shameema Alam[4], Syed S. A. H. Razvi[5]*, Byru Jyothi[6]

[1]Sri Lakshmi Narayana Institute of Medical Sciences, Pondicherry, India
[2]Government Medical College, Srinagar, Jammu and Kashmir, India
[3]Al-Ameen Medical College, Bijapur, Karnataka, India
[4]Dubai Medical University, Dubai, UAE
[5]Khaja Banda Nawaz Teaching and General Hospital, Gulbarga, Karnataka, India
[6]Government Medical College, Bhupalpally, Telangana, India

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***Correspondence:**
Dr. Syed S. A. H. Razvi,
E-mail: shahalisyed193@gmail.com

ABSTRACT

Background: Multidrug-resistant tuberculosis (MDR-TB) poses a major challenge to tuberculosis control, particularly in high-burden countries like India. Treatment of MDR-TB requires prolonged use of second-line anti-tubercular drugs, which are frequently associated with adverse drug reactions. These adverse drug reactions (ADRs) can adversely affect treatment adherence, increase morbidity, and compromise overall treatment outcomes, highlighting the importance of systematic pharmacovigilance. Aim of the study was to analyze the pattern, frequency, and spectrum of adverse drug reactions associated with anti-tubercular drugs in patients with MDR-TB.

Methods: A retrospective descriptive study was conducted among 178 adult MDR-TB patients treated at a tertiary care center between January and December 2024. Patient records were reviewed for demographic details, clinical characteristics, treatment regimens, and reported ADRs. ADRs were categorized by organ system involvement, assessed for causality using the Naranjo scale, and graded for severity using the Hartwig and Siegel scale. Data were analyzed using descriptive statistics.

Results: MDR-TB was more common among males and individuals aged ≤40 years. Endocrine ADRs (18.3%) were the most frequently reported, followed by otic toxicity (14.6%), musculoskeletal complaints (13.5%), and gastrointestinal disturbances (11.4%). Hepatic, dermatological, neurological, and renal ADRs were also observed.

Conclusions: ADRs are common among MDR-TB patients receiving second-line therapy. Early detection, regular monitoring, and strengthened pharmacovigilance are essential to improve treatment adherence and outcomes.

Keywords: Multidrug-resistant tuberculosis, Adverse drug reactions, Second-line anti-tubercular drugs, Pharmacovigilance, Retrospective study

INTRODUCTION

Tuberculosis (TB) remains one of the leading infectious causes of morbidity and mortality worldwide despite decades of global control efforts. According to the World Health Organization (WHO) Global Tuberculosis Report 2024, an estimated 10.6 million people developed TB globally, with India contributing the largest share of the global burden (approximately 27%).[1]

The persistent transmission of TB, compounded by socioeconomic disparities, malnutrition, HIV co-infection, and health system challenges, continues to hinder elimination targets.

Multidrug-resistant tuberculosis (MDR-TB), defined as resistance to at least isoniazid and rifampicin, poses a serious threat to TB control programs.[2] Globally, nearly 410,000 cases of rifampicin-resistant TB were reported in 2023, of which a substantial proportion were MDR-TB. India accounts for one of the highest numbers of MDR-TB cases worldwide.[3]

The emergence of drug resistance is multifactorial, resulting from inadequate treatment regimens, poor adherence, interrupted drug supply, inappropriate prescribing, and pharmacokinetic variability.[4]

Management of MDR-TB requires prolonged administration of second-line anti-tubercular drugs, including fluoroquinolones (levofloxacin, moxifloxacin), injectable aminoglycosides (amikacin, kanamycin), and newer agents such as bedaquiline, delamanid, clofazimine, and linezolid.[5] Although these regimens have significantly improved bacteriological conversion and survival rates, they are associated with a high frequency of adverse drug reactions.[6] Second-line agents are known to produce toxicities affecting multiple organ systems, including ototoxicity, nephrotoxicity, hepatotoxicity, peripheral neuropathy, myelosuppression, QT interval prolongation, and endocrine disturbances.[7,8]

Adverse drug reactions (ADRs) in MDR-TB patients are of particular concern because treatment duration typically extends from 9 to 20 months. The cumulative toxic burden often leads to treatment interruption, dose modification, regimen alteration, non-adherence, and increased risk of treatment failure or amplification of resistance.[9]

Studies have reported ADR incidence rates ranging from 30% to over 70% in MDR-TB cohorts.[10,11] Furthermore, patients with comorbidities such as HIV infection, malnutrition, alcoholism, and diabetes are at heightened risk of drug toxicity due to polypharmacy and altered drug metabolism.[12]

Pharmacovigilance plays a pivotal role in the early detection, documentation, and management of ADRs. The Pharmacovigilance Programme of India (PvPI) emphasizes systematic monitoring of anti-tubercular drug safety, particularly in high-burden settings.[13] However, real-world data on the spectrum, frequency, and severity of ADRs associated with contemporary MDR-TB regimens, including bedaquiline-based therapies, remain limited in many tertiary care settings.

Given the substantial burden of MDR-TB in India and the potential impact of ADRs on treatment outcomes, this study was undertaken to evaluate the pattern, frequency, and system wise distribution of ADRs among patients receiving second-line therapy for MDR-TB in a tertiary care hospital. Understanding these patterns may contribute to strengthening pharmacovigilance systems and optimizing patient-centered TB care.

METHODS

A retrospective descriptive study was conducted at Sri Lakshmi Narayana Medical College to evaluate adverse drug reactions associated with second-line anti-tubercular therapy in patients with multidrug-resistant tuberculosis. The study included adult patients aged 18 years and above who were diagnosed with sputum-positive MDR-TB and received treatment during the period from January 2024 to December 2024.

A total of 178 patients with complete clinical, treatment, and pharmacovigilance records were enrolled. Patients below 18 years of age, those with incomplete documentation, and ADRs not attributable to anti-tubercular drugs were excluded from the analysis. Relevant data were extracted from patient case records, treatment cards, and pharmacovigilance reporting forms, including demographic characteristics, comorbidities, treatment regimens, duration of therapy, number of drugs administered, and documented ADRs.

Adverse drug reactions were classified according to the affected organ system and assessed for causality using the Naranjo probability scale, while severity was graded using the Hartwig and Siegel severity assessment scale.

Data was entered and analyzed using statistical package for the social sciences (SPSS) software, and results were expressed as frequencies and percentages. Logistic regression analysis was performed to identify factors associated with the occurrence of ADRs, with a $p<0.05$* considered statistically significant.

RESULTS

Out of 178 MDR-TB patients, 61.8% were aged ≤40 years, indicating a predominance of disease among younger adults. Males constituted 73.0% of the study population. A significant proportion of patients were underweight (40.4%), reflecting poor nutritional status. Alcohol consumption was reported in 69.7%, while 47.2% were smokers (Table 1). Most patients (73.0%) were diagnosed with MDR-TB within the previous three months. HIV co-infection was present in 51.7% of cases. Slightly more than half (53.9%) were previously treated TB cases. The most commonly used regimen was Regimen 1 (56.7%), followed by Regimen 2 (28.7%) and bedaquiline-based Regimen 3 (14.6%). More than half of the patients (52.2%) received treatment for longer than nine months (Table 2). A wide range of ADRs involving multiple organ systems was observed. Endocrine manifestations (18.3%) were the most frequently reported, followed by otic toxicity with hearing loss (14.6%), musculoskeletal symptoms (13.5%), and gastrointestinal disturbances (11.4%). Hepatic (7.4%), dermatological (7.1%), and central nervous system ADRs (8.0%) were also notable. Less frequent but clinically significant ADRs included renal injury, ocular disturbances, hematological abnormalities, and cardiovascular symptoms (Table 3).

Table 1: Demographic characteristics.

Variable	Category	Frequency (N)	Percentage (%)
Age (years)	≤40	110	61.8
	≥41	68	38.2
Gender	Female	48	27.0
	Male	130	73.0
Body mass index (kg/m²)	Underweight	73	40.4
	Normal	105	59.6
Marital status	Single	40	22.5
	Married	96	53.9
	Divorced/widowed	42	23.6
Education level	None	57	32.0
	Primary	63	35.4
	Secondary/tertiary	58	32.6
Alcohol use	No	54	30.3
	Yes	124	69.7
Smoking status	No	94	52.8
	Yes	84	47.2

Table 2: Drug-disease characteristics.

Variable	Category	Frequency (N)	Percentage (%)
Previous allergies	No	176	98.9
	Yes	2	1.1
Previous ADR history	No	133	74.7
	Yes	45	25.3
Duration since MDR-TB diagnosis (months)	<3	130	73.0
	3–6	22	12.4
	>6	26	14.6
Comorbidities	HIV	92	51.7
	Non-HIV	86	48.3
Treatment category	Naïve	82	46.1
	Previously treated	96	53.9
Treatment regimen	Regimen 1	101	56.7
	Regimen 2	51	28.7
	Regimen 3	26	14.6
Treatment duration (months)	≤9	85	47.8
	>9	93	52.2
Total number of drugs	<5	111	62.4
	≥5	67	37.6

Table 3: Types of ADRs.

ADR category	Frequency (N)	Percentage (%)	Common manifestations
Endocrine	69	18.3	Electrolyte imbalance
Otic	55	14.6	Hearing loss
Musculoskeletal	51	13.5	Back pain
Gastrointestinal	43	11.4	Nausea
CNS	20	8.0	Rash
Hepatic	38	7.4	Itching
Dermatological	27	7.1	Numbness
Peripheral nervous system	20	5.3	Tingling
Renal	15	4.0	Kidney injury
Ocular	14	3.7	Visual disturbances
Hematologic	12	3.2	Anaemia

Continued.

ADR category	Frequency (N)	Percentage (%)	Common manifestations
Cardiovascular	11	2.9	Palpitations
Miscellaneous	03	0.8	Pain

DISCUSSION

The present study demonstrates a substantial burden of adverse drug reactions among patients receiving second-line therapy for MDR-TB. The predominance of younger adults and male patients in this cohort is consistent with national epidemiological data showing higher TB incidence among economically productive age groups and males, possibly due to occupational exposure, substance use, and delayed healthcare-seeking behavior.[1,3]

A notable proportion of patients in this study were underweight, reflecting the bidirectional relationship between malnutrition and tuberculosis. Malnutrition impairs cell-mediated immunity and predisposes individuals to TB infection and disease progression, while active TB further exacerbates nutritional depletion.[14] Undernutrition may also increase susceptibility to drug toxicity by altering drug distribution and metabolism.

Alcohol consumption and smoking were highly prevalent in the present cohort. Both are established risk factors for TB acquisition and poor treatment outcomes. Alcohol, in particular, increases the risk of hepatotoxicity and may interfere with adherence to prolonged MDR-TB regimens.[15] Smoking has been associated with delayed sputum conversion and increased relapse rates.[4]

Endocrine ADRs were the most frequently observed category in this study. Electrolyte imbalances, particularly hypokalemia and hypothyroidism, have been reported with ethionamide, para-aminosalicylic acid, and bedaquiline-containing regimens.[8] Thyroid dysfunction during MDR-TB therapy has been documented in multiple studies, with prevalence rates ranging from 10–30%.[11] Regular thyroid function monitoring is therefore recommended during prolonged therapy.

Ototoxicity was the second most common ADR. Aminoglycosides such as amikacin and kanamycin are well known for causing irreversible sensorineural hearing loss due to cochlear hair cell damage.[7] Duggal and Sarkar reported significant audiometric deterioration in MDR-TB patients receiving injectable therapy, underscoring the need for routine audiological monitoring.[7] The WHO's transition toward all-oral regimens aims to reduce such toxicity.[5]

Musculoskeletal complaints and gastrointestinal disturbances were also frequently reported. Linezolid-associated myopathy and fluoroquinolone-related arthralgia may contribute to musculoskeletal symptoms.[6] Gastrointestinal intolerances is commonly associated with ethionamide, clofazimine, and para-aminosalicylic acid.[10] Although often non-life-threatening, these ADRs significantly impair quality of life and may compromise adherence.

Hepatic ADRs observed in this study may be attributable to the cumulative hepatotoxic potential of multiple anti-TB agents. Although first-line drugs are classically associated with hepatotoxicity, second-line drugs, including fluoroquinolones and ethionamide, can also contribute.8 The coexistence of HIV infection in over half of the study population likely amplified ADR risk due to overlapping toxicities and drug–drug interactions with antiretroviral therapy.[12]

Neurological manifestations, including peripheral neuropathy and CNS symptoms, may be linked to linezolid and cycloserine therapy.[6] Myelosuppression, though less frequent, is a recognized complication of prolonged linezolid use.[5] Cardiovascular manifestations such as palpitations may be related to QT interval prolongation, particularly with bedaquiline and fluoroquinolones.[5,8]

The findings of this study are comparable with those of Prasad et al, who reported a high incidence of ADRs among patients on second-line regimens, with gastrointestinal and neurological events being prominent.[10] Similarly, Isaakidis et al documented frequent treatment modifications due to ADRs in MDR-TB cohorts.[11] These observations collectively highlight the toxic burden associated with MDR-TB therapy.

The high prevalence of ADRs in the present study reinforces the need for structured pharmacovigilance systems, regular laboratory monitoring, patient education, and early intervention strategies. Transition toward shorter, all-oral, individualized regimens as recommended by the WHO may help reduce toxicity and improve adherence.[5] Multidisciplinary collaborations between pulmonologists, pharmacologists, and HIV specialists is essential for comprehensive management.

CONCLUSION

The study demonstrates that adverse drug reactions are highly prevalent among patients receiving second-line anti-tubercular therapy for MDR-TB. Endocrine, otic, musculoskeletal, and gastrointestinal ADRs were the most commonly encountered. Factors such as prolonged treatment duration, multiple drug regimens, malnutrition, alcohol use, and HIV co-infection contribute significantly to ADR occurrence. Strengthening pharmacovigilance systems, ensuring regular monitoring, and adopting patient-centered management strategies are essential to improve treatment adherence and outcomes in MDR-TB patients.

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