Section: Pulmonary Medicine

Original Research Article

TO STUDY THE EFFICACY AND ADVERSE DRUG REACTION ASSOCIATED WITH SHORTER ORAL REGIMEN ON DRUG RESISTANT TUBERCULOSIS

Krutesh Tripathi[1], Ketul Patel[2], Zinal Dave[3], Naisargi Patel[4], Sanket Mistry[2]

[1]*Assistant Professor, Department of Respiratory Medicine, B J Medical College, Civil Hospital, Ahmedabad, Gujarat, India*
[2]*Senior Resident, Department of Respiratory Medicine, B J Medical College, Civil Hospital, Ahmedabad, Gujarat, India*
[3]*Assistant Professor, Department of General Medicine, B J Medical College, Civil Hospital, Ahmedabad, Gujarat, India*
[4]*3rd Year Resident Doctor, Obstetrics and Gynecology, GMERS Sola Hospital, Ahmedabad, Gujarat, India*

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Corresponding Author:
Dr. Zinal Dave,
Assistant Professor, Department of General Medicine, B J Medical College, Civil Hospital, Ahmedabad, Gujarat, India
Email: zinaldave7@gmail.com

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ABSTRACT

Background: Multidrug-resistant tuberculosis (MDR-TB) remains a significant global public health challenge, with India bearing a high burden of cases. In response, shorter all-oral regimens have been introduced to improve treatment outcomes and adherence. However, the efficacy and safety profile of these regimens require thorough evaluation. The objective is to assess the efficacy of the shorter oral regimen in MDR-TB patients and to evaluate the frequency, severity, and nature of adverse drug reactions (ADRs) associated with this regimen.

Materials and Methods: This prospective observational study was conducted at the Department of Respiratory Medicine, over a period of 15 months. A total of 106 bacteriologically confirmed MDR-TB patients, diagnosed via CBNAAT and DST, were enrolled and treated with a standardized shorter oral MDR-TB regimen under the National Tuberculosis Elimination Program (NTEP). Data on demographic characteristics, clinical outcomes, ADRs, and drug resistance patterns were collected and analyzed.

Results: Among the 106 patients, 66.5% were male and the mean age was 42.4 years. The majority (89.6%) had pulmonary TB. ADRs were observed in 81.1% of patients, with gastrointestinal upset (73.2%) being the most common. Other ADRs included hepatic toxicity (17.4%), arthralgia (8.1%), and psychiatric symptoms (3.5%). Most ADRs were mild (76.7%) and manageable. Treatment outcomes showed a high success rate, with a majority of patients either cured or having completed treatment successfully. A small proportion experienced treatment failure, death, or were lost to follow-up.

Conclusion: The shorter oral regimen for MDR-TB demonstrated good efficacy with an acceptable safety profile. Most adverse reactions were mild and manageable, supporting the continued use of this regimen under close monitoring. Timely identification and management of ADRs are crucial for treatment success and patient adherence.

Keywords: Multidrug-resistant tuberculosis (MDR-TB), Adverse drug reaction, Shorter oral regimen

INTRODUCTION

Multidrug-resistant tuberculosis (MDR-TB), defined as resistance to at least isoniazid (H) and rifampicin (R)—the two most potent first-line anti-TB drugs—poses a serious challenge to TB control programs globally. The emergence of rifampicin-resistant TB (RR-TB) and MDR-TB complicates treatment, requiring longer, more toxic, and costlier regimens. In 2019, WHO estimated that globally only 57% of MDR/RR-TB patients who initiated treatment achieved successful outcomes,[1] while the rest experienced death, treatment failure, or were lost to follow-up.

WHO and NTEP have introduced shorter all-oral MDR-TB regimens to improve treatment adherence

and outcomes. These regimens eliminate the need for injectable drugs and aim to reduce toxicity and treatment duration, typically spanning 9–11 months. Bedaquiline-based regimens, now widely adopted, have shown promising results in terms of bacteriological conversion and patient tolerability.[2,3] However, despite the benefits, adverse drug reactions (ADRs) remain a significant concern. Timely recognition and management of these ADRs are essential to ensure treatment continuity and prevent regimen modifications or discontinuation.

MATERIALS AND METHODS

This prospective observational study was conducted at the Department of Respiratory Medicine, over a period of 15 months. A total of 106 bacteriologically confirmed MDR-TB patients, diagnosed via CBNAAT and DST, were enrolled and treated with a standardized shorter oral MDR-TB regimen under the National Tuberculosis Elimination Program (NTEP). Data on demographic characteristics, clinical outcomes, ADRs, and drug resistance patterns were collected and analyzed.

Inclusion Criteria

- Age ≥18 years
- Bacteriologically confirmed TB with rifampicin resistance on CBNAAT or DST
- Willingness to provide informed written consent
- Willingness to attend scheduled follow-up visits
- Presence of comorbidities such as type 2 diabetes mellitus or HIV (if applicable)

Exclusion Criteria

- Were below 18 years of age
- Declined to give informed consent
- Had significant comorbidities such as hypertension, ischemic heart disease, chronic liver or renal disease
- Had prior exposure to second-line anti-TB drugs (used in the shorter regimen) for more than 1 month
- Were pregnant or lactating
- Were unwilling to follow up regularly

RESULTS

In our study, 71 patients (66.5%) were males, while 35 patients (33.5%) were females. Out of 106 patients, 95 patients (89.6%) had Pulmonary Tuberculosis (TB), while only 11 patients (10.3%) had Extra-pulmonary TB.

In the current study, 53 patients (50.2%) did not have any co-morbidity. Among the remaining patients, 25 patients (23.5%) had Type 2 Diabetes Mellitus (DM), 16 patients (15.0%) were HIV positive, and 6 patients (5.6%) had Alcoholic Liver Disease.

Regarding drug resistance, 82 patients (77.4%) had only Rifampicin resistance, while the remaining 24 patients (22.6%) had both Rifampicin and Isoniazid (KatG) resistance on First-line LPA.

Out of the total 106 patients, 86 individuals (81.1%) experienced adverse drug reactions (ADRs) during their therapy, whereas 20 patients (18.8%) did not report any ADRs. Among those who developed ADRs, 37 patients had only one ADR, while the remaining 49 patients developed two or more ADRs.

Table 1: Distribution of patients according to type of ADR

Adverse Drug Reaction (ADR)	Number of Patients (n = 86)	Percent (%)
GI upset (Diarrhea/Nausea/Vomiting)	63	73.2%
Hepatic	15	17.4%
Arthralgia	7	8.14%
Optic neuritis	2	2.33%
Peripheral neuropathy	6	6.98%
Dermatological	2	2.33%
Headache	3	3.49%
Hypothyroidism	1	1.16%
Psychiatric	3	3.49%
ECG Changes (QT prolongation)	4	4.65%

Table 2: ADR and offending drug involved

Adverse Drug Reactions (ADR)	Offending Drug Involved
GI upset (Diarrhoea/Nausea/Vomiting)	Eto, Z, H, E, Bdq
Hepatotoxicity	Eto, Z, H, Bdq
Arthralgia	Z, FQ, Bdq
Peripheral Neuropathy	H, FQ
Skin Reaction	Any drug can be involved (mainly Cfz)
Headache	Z, Eto, Bdq
Hypothyroidism	Eto
Psychiatric Symptoms	H, FQ
Optic Neuritis	E, Eto
ECG Changes (QT Prolongation)	Bdq, FQ, Cfz

After random stoppage and then sequential re-introduction of the drugs, it was found that Eto and Z were mainly the offending drug for causing GI upset and Hepatotoxicity. Z was again associated with causation of Arthralgia. Cfz was involved in some

skin reactions. Bdqfq, CFz causing cardiac toxicity (ECG changes).

Table 3: Distribution of patients according to ADR and offending drug

Offending Drug	Number of Patients (n = 86)	Percent (%)
Eto	72	83.7%
H	21	24.4%
FQ	7	8.1%
Z	75	87.2%
E	48	55.8%
Cfz	6	6.9%
Bdq	4	4.65%

Treatment Response and Radiological Improvement: In our study, 42 patients (39.6%) achieved sputum conversion to negative by the end of the first month, while 18 patients (20%) still had positive smear microscopy and culture at the end of the Intensive Phase (IP). By the end of the sixth month of treatment, only 6 patients (8.2%) remained positive on smear microscopy and culture, and they were classified as treatment failures.

At the end of the IP phase, 73 patients (81.2%) showed significant improvement in their chest X-ray (CXR) findings, while 17 patients (18.8%) showed no radiological improvement. By the end of the sixth month of treatment, 64 patients (87.6%) had improvement in CXR findings, whereas 9 patients (12.3%) showed no significant radiological improvement.

There was a significant association between the final treatment outcome and improvement in clinical and radiological (CXR) findings during treatment (p-value < 0.001). The majority of patients who gained weight and demonstrated clinical as well as CXR improvement during treatment were cured.

Table 4: Association between Outcome and ADR in patients on Shorter MDR-TB regimen

Outcome	ADR Present	ADR Absent	P value
Cured	44	16	P value: 0.34
Expired	5	0	
Loss to follow-up	6	0	
On AKT	8	4	
Shifted to All Oral Longer Regimen	14	4	
Treatment Failure	4	1	
Chi-square = 5.59, df = 5			

There was no significant association between the occurrence of adverse drug reactions (ADRs) and the treatment outcome (p-value = 0.34). Out of 60 patients who were cured with the shorter regimen for MDR-TB, 44 patients (73.3%) developed ADRs during the course of treatment.

DISCUSSION

Adverse Drug Reactions (ADRs)

ADRs were reported in 81.1% of patients, with gastrointestinal disturbances (73.2%) being the most common, followed by hepatotoxicity (17.4%) and arthralgia (8.1%). This high ADR incidence is in line with global findings, though slightly higher than the 64% reported by Rohan Hire et al. and 72% by Arif Dela. Notably, multiple ADRs occurred in more than half of affected patients, underlining the importance of routine pharmacovigilance.

Key offending drugs included pyrazinamide (87.2%), ethionamide (83.7%), and ethambutol (55.8%). Although most ADRs were mild and manageable, 5.8% of patients required permanent drug discontinuation. Common psychiatric symptoms, though rare (3.49%), require special attention due to the risk of non-adherence.[4-6]

No statistically significant correlation was found between ADR occurrence and treatment outcomes (p=0.34), suggesting that effective management of ADRs can prevent poor outcomes.

Treatment Outcomes

Cure was achieved in 56.7% of patients, while 16.9% were shifted to longer regimens, and 11.3% were still on treatment at study completion. Mortality (4.7%) and treatment failure (4.7%) were relatively low, comparing favorably with outcomes from Sangita Patel (33.1% cured, 29.7% mortality) and Arif Dela (47.2% cured, 22.8% mortality). These results demonstrate improved efficacy and tolerability of the shorter regimen.[7,8] Importantly, a statistically significant association was observed between treatment success and improvement in weight, clinical symptoms, and CXR findings (p<0.001). These markers should be routinely monitored to evaluate treatment response. However, no significant association was found between treatment outcome and ADR occurrence, indicating that proper ADR management does not compromise treatment efficacy.[9]

Comparative Outcomes

Study	Cure (%)	Death (%)	Default (%)	Treatment Failure (%)
Our Study	56.7	4.7	5.6	4.7
Vishakha K. Kapadia	45.1	25.5	20.0	8.8

Arif Dela	47.2	22.8	13.6	10.4 (XDR progression)
Prasanta Das	44.3	3.9	13.7	4.9

The relatively higher cure rate and lower mortality in our study support the feasibility of implementing shorter oral regimens in national TB control programs, especially when ADR monitoring systems are in place. These findings are consistent with results from Udwadia et al., who also reported encouraging outcomes with individualized MDR-TB treatment in the Indian private sector, despite the challenges of ADRs and regimen complexity.[10]

CONCLUSION

Proactively preventing adverse drug reactions (ADRs) is consistently more efficacious than intervening after the ADRs have already taken place. Therefore, the only way to reduce toxicity is by careful monitoring of both recognized and unrecognized adverse drug reactions, evaluating their causal relationship, and promptly addressing them. Monitoring laboratory and clinical indicators and implementing appropriate strategies can help decrease the incidence and severity of recognized adverse drug reactions (ADRs). This may aid in enhancing the adherence and eventually the standard of patient care. Therefore, it is crucial to closely monitor and promptly manage the medication in order to ensure adherence and ultimately enhance the outcome in cases of multidrug-resistant tuberculosis (MDR-TB). During our investigation, the most adverse reaction noted was gastrointestinal disturbance resulting from unregulated diarrhea, nausea, or vomiting. Additional side events included arthralgia, hepatotoxicity, peripheral neuropathy, skin reaction, mental symptoms, headache, and hypothyroidism.

Further it was found that there was significant improvement in clinical parameters as wellasCXRfindingsduringthecourseofthetreatmentin thosewhowerecured.There was no significant enhancement in clinical indicators and chest X-ray results during treatment among those who had treatment failure and those who expired.

Cause of death was not due to ADR suffered, but due to other causes, such as comorbidities and addictions, mortality associated with MDR-TB, non-compliance with AKT, cachexia, nutritional deficiency, cardio-pulmonary arrest.

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