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Research Article

Pattern of Adverse Drug Reactions and its Potential Impact on Drug Resistant Tuberculosis Patients at a Tertiary Care Teaching Hospital in Western India

Amin S[1], Mishra V[1], Desai Mira[1] and Solanki Rajesh[2]*

[1]Department of Pharmacology, BJ Medical College & Civil Hospital, India

[2]Department of Pulmonary Medicine, BJ Medical College & Civil Hospital, India

Abstract

Objectives: To evaluate Adverse Drug Reactions (ADRs) pattern of antitubercular drugs and its impact on MDR & XDR-TB patients.

Material & methods: An observational, continuous, retrospective & prospective, multi-centered study was carried out in MDR & XDR-TB patients enrolled for DOTS-PLUS regimen at Department of Pulmonary Medicine, Civil Hospital, Ahmedabad, over a period of 24 months from October 2015 to September 2017. Demographical details, clinical presentation of ADRs, causal drugs, seriousness, outcome, causality, severity and preventability were recorded in a case record form.

Results: A total 202 ADRs were reported in 155 patients, majority in initial 31 days to 90 days (88, 43.56%) of starting the drug treatment and were serious (101, 54.46%). Majority of the patients were treatment experienced and with mean age 35.92 ± 1.07 years. Most common causal drug was ethionamide (52, 18.98%) followed by kanamycin (47, 17.15%) and pyrazinamide (38, 13.87%). Commonly reported ADRs were altered liver function tests (30, 14.85%) followed by vomiting & nausea (26, 12.87%) and difficulty in hearing (21, 10.40%). Further, kanamycin was the most common causal drug withdrawn permanently due to disability. Surprisingly, half of the patients received drugs at low (89, 36.1%) and high end (72, 26.2%) of recommended dose range. Several (100, 49.50%) ADRs were continuing till the end of the study. Most of the ADRs were reported late and non preventable (125, 61.88%) and moderately severe (106, 52.48%) in nature.

Conclusion: Pyrazinamide, ethionamide and kanamycin are major culprit drugs for severe, serious either chronic or irreversible ADRs in DR-TB patients resulting into frequent treatment interruptions and disability. Use of two weight band regimens (<45 Kgs and >45 Kgs) reduces the flexibility of dose adjustment and thereby exposes the patient to high dose resulting in ADRs. A substantial number of ADRs are reported in late stage indicating that the early warning signals are missed or not reported by health care workers or even ignored by patient themselves. Hence, careful monitoring during initial period can help in early identification and treatment of these ADRs. Pre-treatment liver function test, thyroid function test, renal function test and audiogram should be mandatory for identifying high risk patients. There is a need to consider individualized treatment regimen and a substitute for kanamycin (due to irreversible damage) to reduce ADRs for a successful treatment outcome.

Keyword: Tuberculosis; Multidrug resistant; Adverse drug reactions; Extensively drug resistant; HIV/AIDS

Introduction

Medicines are double edged sword that may result into beneficial as well as undesirable/harmful effects like Adverse Drug Reactions (ADRs) [1]. They are important cause of morbidity and mortality in patients accounting for about 100,000 deaths annually and are estimated to be 4th to 6th largest cause of death in USA [2]. Tuberculosis (TB) is the world's second commonest cause of death from infectious disease, after HIV/AIDS and India accounts for nearly 1/3rd of global tuberculosis burden. Out of the 8.6 million TB cases worldwide, 2.2 million (25%) cases are in India, making India the country with highest TB burden [3]. Several patient and drug factors has led to resistance to first line anti TB drugs resulting into Multi Drug Resistant Tuberculosis (MDR-TB) & Extensively Drug Resistant Tuberculosis (XDR-TB) [4]. The incidence of ADRs with anti-tubercular drugs is varies from 5% to 50% requiring either modification of treatment or stoppage of the drug therapy [5]. In addition, ADRs can lead to frequent treatment interruption and results into avoidable morbidity, drug-resistance, treatment failure and reduced quality of life. Often the ADRs are mild to moderate in nature and initiate with warning signals which needs to be captured by close monitoring of the patients [6]. Whereas, ADRs, which are serious and require interventions, are reported or noticed late in course of therapy and these ADRs may be irreversible resulting in disability or permanent damage. Therefore, ADRs during the course of anti-tubercular treatment are of significant medical importance and should be routinely monitored. In view of multi drug therapy with high rate of serious and irreversible toxicity and long duration of treatment, MDR-TB & XDR-TB being of national importance, the present study was conducted with following aims and objectives to evaluate ADRs for clinical spectrum, risk factors, outcome and analyze specific organ toxicity in the patients of drug resistant TB.

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***Corresponding author:** Desai Mira, Department of Pharmacology, BJ Medical College & Civil Hospital, Ahmedabad, India, E-mail: desaimirak@yahoo.in

Materials and Methods

This was an observational, continuous, retrospective and prospective, multi-centered study carried out in patients of Multidrug Resistant (MDR) and Extensively Drug Resistant (XDR) TB enrolled at Department of Pulmonary Medicine, Civil Hospital, Ahmedabad and DOTS centers, Ahmedabad for a period of 24 months. Prior approval of the study was obtained from Institutional Ethics Committee (IEC). All the details of ADRs were recorded in a pretested case record form. The patients were followed up either personally or telephonically till the resolution of ADRs or till the end of the study duration. The data was analyzed for patient factors, clinical spectrum, causal drugs, risk factors, duration, seriousness, outcome, causality, severity and preventability of ADRs.

Results

Patient factors

A total of 1,060 patients were treated for MDR & XDR-TB during the study period. Out of these, 202 ADRs were reported in 155 (14.62%) patients. Out of 155 patients, 84 (54.19%) were men and 71 (45.81%) were women with men to women ratio of 1.83:1 (M:W) and mean age 35.92 ± 1.07 years (mean ± SEM). Majority of the patients (107, 69.03%) belonged to 16 years to 45 years of age group with mean body weight 45.03 ± 13.16 kilograms (mean ± SD). Co-morbidities such as HIV infection (11, 7.10%), hypertension plus diabetes (6, 3.87%) and infective hepatitis (6, 3.87%) were also observed. Family history for tuberculosis was positive in 20 (12.90%) patients. Out of 155, 93 (60%) patients were previously treated for TB. Majority of the patients (91, 58.71%) were being treated for MDR-TB, followed by XDR-TB (58, 37.41%) and mono-H resistant TB (6, 3.87%) (Table 1).

Table 1: General characteristics MDR & XDR-TB patients in the study (n=155).

Parameters	MDR & XDR-TB patients with ADRs (n=155) (%)
Personal History	
Alcoholic	11 (7.10)
Tobacco chewing + Smoking	7 (4.52)
Alcoholic + Smoking	6 (3.87)
Smoking	5 (3.23)
Tobacco chewing	3 (1.94)
No habits	123 (79.35)
Co-morbid diseases	
HIV positive	11 (7.10)
Hypertension + Diabetes	6 (3.87)
Hypertension	4 (2.58)
Hepatitis C	3 (1.94)
Diabetes	2 (1.29)
Hepatitis E	2 (1.29)
Cataract	1 (0.65)
Hepatitis B	1 (0.65)
Family history of TB	**20 (12.90)**
Details of previous TB treatment	**93 (60)**
Treatment defaulter	50 (32.36)
Treatment failure	30 (19.35)
Treatment completed	13 (8.39)
Types of tuberculosis	
MDR-TB	91 (58.71)
XDR-TB	58 (37.41)

Drug factors

5.2.1. Causal drugs: A total 274 drugs were suspected to cause 202 ADRs. Out of these, most of the drugs were administered orally (213, 77.74%) followed by intramuscularly (61, 22.26%). Most common causal drug was ethionamide (52, 18.9), followed by pyrazinamide (38, 13.87%) and kanamycin (47, 17.15%) (Table 2). Interestingly, it was observed that 103 (50.9%) drugs were administered in appropriate dose (mg/kg) while 99 (36.1%) towards lower end of recommended dose and 72 (26.2%) drugs towards higher end of recommended dose range.

Clinical presentation: Out of 155 patients with ADRs, 38 (24.52%) developed more than one ADR. Out of 202 ADRs, 30 (14.85%) were altered liver function tests followed by vomiting & nausea (26, 12.87%) and difficulty in hearing (21, 10.40%). Most commonly involved body system was gastrointestinal system (39, 19.31%) followed by neurology (33, 16.34%) and hepatobiliary system (30, 14.85%).

Time relationship and duration: Majority of the ADRs (180, 43.56%) were reported in the initial 90 days of starting the drug treatment, while only 22 (10.89%) were seen later than that (Figure 1). At the end of study period, 58 (28.71%) ADRs resolved and majority resolved within 11 days to 30 days after onset, while 38 (26%) continued for 2 months, 42 (29%) for 6 months and 20 (14%) for more than 6 months duration.

Seriousness and outcome: Out of 202 ADRs, 110 (54.46%) were serious in nature wherein majority of the patients required hospitalization (61, 55.45%) and the most common was altered liver function tests (28, 13.9%). By the end of the study period, 100 (49.50%) ADRs were continuing, 58 (28.71%) resolved while 4 (1.98%) cases of ADRs were fatal in nature. Out of 4 deaths, one was drug induced hepatitis while 3 cases, the cause of death was not determined (Figure 2).

Dechallenge & rechallenge: Dechallenge, of causal drugs was done in 127 (62.9%) ADRs. Surprisingly, it was negative in 70 (34.6%), positive in 55 (27.2%) and not known in 2 (0.99%) cases. While the causal drugs was re-administered in 26 (12.9%) cases and interestingly, the outcome was positive in 12 (5.9%), negative in 10 (4.9%) and not known in 4 (1.9%) cases. Kanamycin (27, 13.4%) was the most common permanently withdrawn drug, while pyrazinamide (6, 2.9%) was the most common drug withdrawn temporarily.

Causality, preventability and severity: The causality assessment was done by using both WHO-UMC criteria and Naranjo's scale. Majority of ADRs were categorized as probable (143, 70.79%) in nature as per WHO-UMC criteria while it was possible (125, 61.88%) using Naranjo's algorithm. Out of 7 (3.47%) ADRs with certain causality, 4 (57.14%) were joint pain, 2 (28.57%) were vomiting and one was diarrhea. Preventability assessment of ADRs using modified Schumock and Thornton scale showed that most of the ADRs were non preventable in nature (125, 61.88%). Severity assessment using Hartwig & Siegel's severity assessment scale showed that most of the ADRs were moderately severe in nature (106, 52.48%).

Table 2: Clinical manifestations of ADRs and common causal drugs.

Body system involved (%)	No. of suspected ADRs (n=202) (%)	Common causal drugs (n=274) (%)
Gastrointestinal System 39 (19.3)	Vomiting: 26 (12.9)	Para-amino salicylic acid: 26 (9.49)
		Ethionamide: 23 (8.39)
	Diarrhea: 9 (4.5)	Levofloxacin: 9 (3.28)
		Ethionamide: 9 (3.28)
	Anorexia: 4 (1.98)	Ethionamide: 3 (1.1)
Nervous System 17 (8.4)	Peripheral neuropathy: 12 (5.9)	Isoniazid: 12 (4.38)
		Linezolid: 12 (4.38)
	Burning sensation in feet: 5 (2.5)	Isoniazid: 5 (1.83)
		Linezolid: 5 (1.83)
Hepatobiliary System 30 (14.9)	Altered liver function test: 30 (14.9)	Pyrazinamide: 15 (5.47)
		Ethionamide: 13 (4.75)
Ear, Nose and Special Senses 44 (21.8)	Difficulty in hearing: 21(10.4)	Kanamycin: 22 (8.1)
	Tinnitus: 7 (12.4)	Amikacin: 4 (1.5)
	Vertigo: 16 (7.9)	Kanamycin: 12 (4.38)
		Capreomycin: 3 (1.09)
Urinary System 18 (8.9)	Raised serum creatinine level: 12 (8.9)	Kanamycin: 13 (4.8)
	Hypokalemia: 3 (1.5)	
	Hyponatremia: 2 (0.99)	
	Hypoproteinemia: 1 (0.5)	
Musculoskeletal System 17 (8.4)	Arthralgia: 17 (8.4)	Pyrazinamide: 17 (6.20)
		Ethambutol: 8 (2.92)
Psychiatric System 11 (5.5)	Psychosis: 11 (5.5)	Cycloserine: 10 (3.65)
Endocrine system 8 (3.9)	Hypothyroidism: 8 (3.9)	Para-amino salicylic acid: 8 (2.92)
		Ethionamide: 8 (2.92)
Ophthalmology 8 (3.9)	Blurring of vision: 8 (3.9)	Ethambutol: 8 (2.92)
Dermatology 5 (2.5)	Skin discoloration: 5 (2.5)	Clofazimine: 5 (1.8)
Hematology 5 (2.5)	Anemia: 4 (1.9)	Linezolid: 5 (1.8)
	Thrombocytopenia: 1 (0.5)	

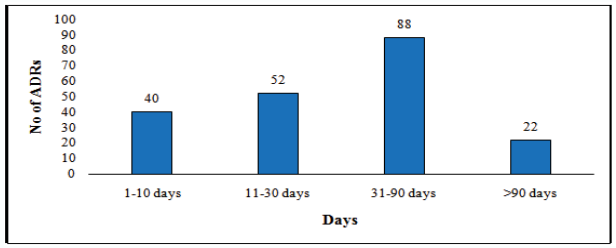

Figure 1: Time relationship between starting of suspected drug and appearance of ADRs in MDR & XDR-TB patients (n=202).

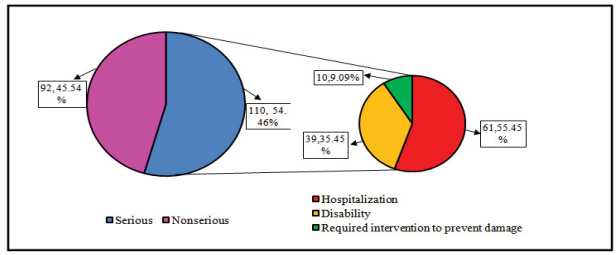

Figure 2: Seriousness of ADRs in MDR & XDR-TB patients (n=202).

Discussion

The present study showed that incidence of ADRs in DR-TB patients is 15%, most common being hepatotoxicity, gastrointestinal problems and ototoxicity. In addition, a substantial number of ADRs are reported in late stage indicating that the early warning signals are missed or not reported by health care workers or even ignored by patient themselves. Consequently, the ADRs observed were serious, severe and non-preventable. Drug resistant tuberculosis requires long term treatment with strict adherence, wherein ADRs can lead to treatment interruptions and adversely affect adherence [7]. Temporary and permanent treatment interruptions were also noted in this study as per dechallenge information. These treatment interruptions can also adversely affect treatment outcome and may increase the chances of drug resistance leading to total drug resistant tuberculosis (TDR-TB) [8,9]. Thus, the present study sheds light on some important factors affecting TB treatment and outcome.

Our study reported more number of men developing ADRs as compared to women (M:W 1.83:1) which is similar to other studies [4,6]. This can be probably because of the fact that men are more mobile due to the work and are thus more exposed to infections. Moreover, being main earning member of the family, they cannot afford to lose their daily wages and thus seek medical treatment by regular and frequent visits to hospital [4]. Further, most of the patients in the study were young which is similar to Gillani et al. [10] and Zala et al. [11] (Table 3). It is likely that this age group are involved in activities like smoking, alcohol intake, etc., which may decrease immunity and increase susceptibility to TB infection and ultimately adversely affecting the outcome of the treatment [4,6]. However, high prevalence of drug resistant TB and ADRs in young population is alarming as this would result in considerable health and financial burden on individual family, state and country as this age group contributes significantly to the economy in terms of manual and intellectual work. In addition, we observed that drug resistant

Table 3: Comparison of general characteristic of patients in different studies.

Parameter	Present Study 2017	Hire et al. [16]	Rathod et al. [18]	Akshata et al. [17]	Gillani et al. [10]	Yee et al. [14]
Location	India (Gujarat)	India (Maharashtra)	India (Maharashtra)	India (Karnataka)	Malaysia	Canada
No. of patients	155	110	265	607	653	430
Type of patients	MDR and XDR TB	MDR TB	MDR TB	MDR TB	Primary TB	Primary TB
Mean age (years)	35.92 ± 1.07	40-49	25-34	>30	18-54	17-94
Gender						
Men	84	83	184	402	464	278
Women	71	27	81	205	189	152
Study Duration (months)	24	9	24	40	30	108

tuberculosis and risk of ADRs was more in treatment experienced patients as compared to treatment naïve patients which is similar as Patel et al. [12]. Sequential exposure to inadequate previous TB treatment can lead to progressive acquisition of drug-resistance mutants leading to drug resistant tuberculosis. Further, drug resistant TB is treated with more toxic second line drugs causing more number of ADRs [4]. Ethionamide, pyrazinamide and kanamycin were the common causal drugs which is similar to studies by Awad Tag et al. [13] and Yee et al. [14].

Several ADRs were severe and serious in nature (110, 54%) involving vital organ systems like hepatobiliary, renal, auditory system. However, majority were reported late when already significant damage was done. This can be possibly due to TB patients being treated at peripheral DOTS centre, often miss the initial warning signs and symptoms of ADRs. ADRs severe enough resulting in incapacitating illness and requiring interventions were noted by health worker and patients are referred to nodal TB centers.

Majority of ADRs were continuing and not recovered till the end of study period, which further supports our observation of serious and irreversible nature of ADRs. Fatal Serious Adverse Event (SAE) was hepatotoxicity during the study period similar to Gholami et al. [15].

As most of the ADRs due to antitubercular drugs are dose-dependent, Dechallenge (reduction of dose or termination) of the causal drugs is essential for the management. In spite of causal drugs being dechallenge in majority of the cases, ADRs continued in most of the cases till the end of the study (negative dechallenge). This supports our observation that ADRs were reported late or in advanced stage and/or may not be dose dependant. Additionally, certain ADRs like hepatotoxicity and ototoxicity require long time to resolve. In our study, kanamycin was the most common permanently withdrawn drug while pyrazinamide was the most common drug withdrawn temporarily. Re-administration of the causal drugs following recovery of the ADR (rechallenge) is usually not attempted due to ethical reasons. However, tuberculosis is one such condition where rechallenge is attempted due to obvious reason. The causal drugs were re-administered following recovery from vomiting, diarrhea, arthralgia and vertigo. Interestingly, re-administration resulted in reappearance of ADRs establishing a definite causal relationship in few cases. The most common positive rechallenge was seen with arthralgia due to pyrazinamide.

Causality, severity and preventability

Majority of ADRs were probable according to WHO-UMC criteria and possible according to Naranjo's scale in our study which is similar to Prajapati et al. [4] and Jain et al. [6]. This can be because of associated comorbidities, multiple drug therapy started simultaneously and negative dechallenge that downgrade the causality score. Majority of ADRs in our study were non-preventable and moderately severe in nature. Conversely, a study by Hire et al. [16] reported that majority of the ADRs were moderately severe and possibly preventable. The difference in preventability may be due to use of different scales in two studies (Schumock and Thornton's *vs.* Hallas' score). While, ADRs like raised serum creatinine level, vertigo, diarrhea and arthralgia were definitely preventable in our study. A detailed history of underlying disease, drug allergy and previous drug reaction before starting the treatment could have prevented these ADRs. Further, anti-tuberculosis drugs (26.2%) were administered in high (mg/kg) end of the recommended dose as per Revised National Tuberculosis Control Program (RNTCP) due to two fixed weight bands (Weigh <45 kg and weight >45 kg) up to July 2017 [3]. Two weight bands reduces the flexibility of dosage adjustment in patients and presumably to high dosage. This increases chances of severe ADRs resulting into treatment interruptions, discontinuation and hospitalization which ultimately decrease the successful outcome of a treatment regimen.

ADR analysis

The most common clinical presentation of ADRs were altered liver function tests, vomiting, hearing loss, etc., is similar to published studies (Table 4) [15,16]. The most common causal drugs for altered liver enzymes were pyrazinamide and ethionamide. Although, the exact mechanism of hepatic injury by pyrazinamide is not well known, the drug is extensively metabolized in liver and its metabolites are responsible for hepatic injury. Moreover, high doses of pyrazinamide prescribed in DR-TB increases the vulnerability and risk of hepatotoxicity [17,18]. Similarly, ethionamide being extensively metabolized by the liver can cause liver injury due to toxic or immunologically active metabolites [19]. Our study observed that majority of the patients with hearing loss and tinnitus were young (16 years to 45 years) which is synonymous to other available studies [20,21]. Hearing loss and tinnitus being usually uncommon in young population, increases the plausibility of drug induced ototoxicity. In addition, we found that hearing loss was more common in patients with history of previous TB treatment which is consistent with Bardien et al. [22]. It has been reported that prior exposure to aminoglycoside especially kanamycin and streptomycin is a risk factor for hearing loss. Most common causal drug for hearing loss and tinnitus was kanamycin in our study which was similar to Rathod et al. [18]. Moreover, hearing loss was usually seen within 31 days to 90 days of drug therapy. These observations emphasize the need of audiometry,

Table 4: Comparison of common ADRs and causal drugs with other studies.

Parameters	Present study 2017	Hire et al. [16]	Rathod et al. [18]	Gillani et al. [10]
Location	India (Gujarat)	India (Maharashtra)	India (Maharashtra)	Malaysia
Type of patients	MDR and XDR TB	MDR TB	MDR TB	Primary TB
Common ADR	Altered liver enzymes	Nausea and Vomiting	Nausea, vomiting and anorexia	Rash and itching
Body system involved	Liver and biliary system	Gastrointestinal System	Gastrointestinal System	Skin and appendages
Causal drugs	Pyrazinamide	Ethionamide	NA	Pyrazinamide
	Kanamycin	Fluoroquinolones		Ethambutol
Time relationship	1-3 months	1-2 months	1-2 months	NA

close monitoring and patient education especially in early months (1 month to 3 months) for early detection and mitigation of hearing loss [23].

Nausea and vomiting due to PAS and ethionamide reported in our study are similar to other published studies [17,24]. Oral administration of drugs is likely to cause gastrointestinal ADRs such as vomiting, diarrhea and anorexia. Gastrointestinal ADRs are usually mild in nature but requires immediate symptomatic treatment while prolonged severe vomiting and diarrhea can cause dehydration, electrolyte imbalance and metabolic alkalosis that may require stoppage of causal drugs [25]. Vertigo due to kanamycin has been reported within first 10 days of treatment. Hire et al. [16] has reported that kanamycin has definite causal relationship with vertigo due to possible induction of free radical injury to inner hair cells by kanamycin. Majority of the patients with arthralgia were young, which rules out other causes like osteoarthritis and osteoporosis. Pyrazinamide is known to precipitate produces arthralgia and arthritis by increasing serum uric acid levels [26]. Peripheral neuropathy due to isoniazid and linezolid was observed in the initial 90 days after starting treatment which is similar to other published studies [16,24]. Psychiatric illness is well documented ADR of cycloserine which was reported in 10 (6.5%) patients in our study. Nephrotoxicity in the form of raised serum creatinine levels was seen in small number of patients in our study. However, it was more as compared to a study by Rathod et al. [18] (7.8% *vs.* 1.1). Raised serum creatinine level due to kanamycin was seen within 30 days of starting the treatment. Thus, nephrotoxicity due to aminoglycosides can be prevented by careful monitoring of serum creatinine level during first month of treatment initiation. Interestingly, eight cases of hypothyroidism due to treatment with ethionamide and PAS within 1 month to 3 months of treatment were also observed, exclusively in women which was similar to a study done by Gupta et al. [27].

Strengths and limitations

This prospective and retrospective study conducted at two centers, wherein, all the information was recorded precisely. The number of patients included in our study represents a sufficiently good sample size considering high prevalence of ADRs in DR-TB. The strength of our study includes recruitment of both MDR-TB and XDR-TB patients who developed ADRs with complete follow up for entire study duration (24 months). Secondly, detailed analysis of all the patient factors responsible for ADRs was performed. Also we have analyzed the drug factors for ADRs like causal drugs, its route of administration and dose, dechallenge and rechallenge of the causal drugs, clinical presentation, causality, severity and preventability of ADRs.

However, like any other study, there were certain limitations. The follow up of the patients has been a great challenge for ADR reporting and its outcome. The patients were diagnosed and started on antitubercular regimen at DR-TB centre, however, the follow up was done at peripheral DOTS centre. It is possible that during the follow up period, mild to moderate ADRs were not captured by health care worker in the treatment card. Also there is always a possibility of missing out ADRs and initial warning signals and actual outcome of the ADRs may not be reflected in each case. Thus, there is a possibility of under reporting.

Conclusion

Pyrazinamide and kanamycin are major culprit drugs for severe irreversible ADRs in DR-TB patients in initial 3 months of treatment. Use of two weight band regimens (<45 kgs and >45 Kgs) reduces the flexibility of dose adjustment and thereby exposes the patient to high dose resulting in ADRs. It was also observed that majority of severe and irreversible reactions are seen in first 90 days after treatment initiation. Hence, careful monitoring during initial period can help in early identification and treatment of these ADRs. Pre-treatment liver function test, thyroid function test, renal function test and audiogram should be mandatory for identifying high risk patients. There is a need to consider individualized treatment regimen to reduce ADRs and for a successful treatment outcome.

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