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TO STUDY OF EFFICACY AND ADVERSE DRUG REACTIONS ASSOCIATED WITH SHORTER REGIMEN OF MULTI DRUG RESISTANT TUBERCULOSIS

Respiratory Medicine

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ABSTRACT

Background : Multidrug-resistant tuberculosis(MDR-TB) has become a global threat concerning to risk of high mortality with the potential to cause adverse drug reactions(ADRs) which if not managed properly may affect patient compliance, resulting in treatment outcome. **Objectives :** To assess the efficacy and adverse drug reactions(ADRs) associated with shorter MDR-TB regimen and the proportion of patient defaulting the shorter drug regimen of MDR-TB due to ADRs. **Material and Methods :** A prospective observational study was carried out on diagnosed Rifampicin resistant tuberculosis enrolled for Shorter drug regimen of MDR-TB at Respiratory medicine department, SMIMER over 15 months and data analysis conducted over 3 months. **Results :** Out of 113 patients, Mean age of the patients was 42.42±16.37 years. 88.5% patients had Pulmonary and 11.5% patients had Extra pulmonary TB. Total 90 patients had developed ADR. Most common ADR was GI upset, detected in 51 (56.6%) patients followed by Arthralgic, Hepatic and Ototoxic symptoms in 20 (22.2%), 19 (21.1%) and 17 (18.8%) patients respectively. 61.9% patients had mild ADR, 11.5% and 6.2% patients suffered moderate and severe ADR respectively. Out of 113 patients, 54% patients were cured, 15% patients were on treatment, 15.9% patients were shifted to all oral longer regimen, 4.4% patients had treatment failure, 4.4% patients expired and 6.2% patients were lost to follow up. **Conclusion :** The frequency and severity of ADRs can reduced by monitoring laboratory, clinical parameters . Thus, close monitoring and timely management are essential for treatment adherence and finally improve outcome in MDR-TB.

KEYWORDS

Adverse drug reactions(ADRs), Multidrug resistant tuberculosis(MDR-TB), National tuberculosis elimination programme (NTEP)

INTRODUCTION

World Health Organization Global TB report 2019 has reported an estimated 33% of new cases and 18% of previously treated cases had MDR/RR-TB. In 2019, an estimated 465000 new cases of MDR/RR-TB emerged globally. MDR/RR-TB caused an estimated 182000 deaths in 2019. Most cases and deaths occurred in India and China. WHO issued a guideline for the management of drug resistant TB in 1996. Programmed management for drug resistant tuberculosis (PMDT) services in India was initiated from August 2007. A standard shorter regimen for MDR-TB treatment has been approved ndia. It is implemented under National Tuberculosis Elimination Programme (NTEP)-National DOTS plus committee. The duration of shorter regimen of MDR-TB is 9 months. Therefore, it is imperative to monitor and treat adverse drug reactions developed by the patients. This approach ensures better compliance of patients and good treatment outcome. The aim of this study was to assess the efficacy and ADR of MDR-TB patients on shorter regimen. This would further enable the health care professionals and management to devise relevant interventions to improve the treatment outcome of the patients, as well as the programme.

Methodology

Study design - This study was a prospective observative study, performed in the department of Respiratory medicine at tertiary care hospital over a period of 18 months. TB patients with the evidence of resistance to Rifampicin by CBNAAT were assessed by enrollment. MDR-TB diagnosed patients of age above 18 years and having HIV and DM as co-morbidities and having all pretreatment investigations as normal were included in the study. Patients under 18 years of age, pregnant or presenting with any other co- morbidities. The study was approved by the institutional ethics committee.

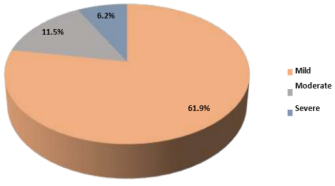
Data Collection- Patient were diagnosed as MDR-TB based on Rifa-resistance result on CBNAAT. Pre- treatment evaluation as per the NTEP guidelines was done. They were counseled and Shorter MDR-TB regimen was started under NTEP and they were asked for follow up after 1st month, end of 4th and 6th month and if they suffered from any adverse drug reaction. Data was collected using predesigned, structured Performa to enter patient details, detailed clinical history, personal history, including presenting complaints, past history of tuberculosis, history of previous hospitalization, history of anti-tubercular treatment, general system examination, respiratory system examination, laboratory investigations, radiological investigations and physical examination of patients who met the inclusion criteria. The Shorter regimen consisted of an intensive phase(IP) of 4-6 months with 7 drugs namely kanamycin (Km), High dose Moxifloxacin (Mx), ethionamide (Eto), Pyrizinamide (Z), ethambutol (E), Clofazimine (Cfz) and high dose Isoniazid (H). This was followed by a continuation phase (CP) of 5 months with 4 drugs, namely High dose Moxifloxacin (Mfx), Clofazimine (Cfz) , Ethambutol (E), Pyrizinamide (Z). The response to the treatment during follow-up were recorded by improvement in clinical parameters, sputum microscopy and culture and radiological improvement. Treatment outcomes : such as cured, default, treatment failure and death as per NTEP definitions were recorded.

RESULTS

Total 113 patients with proven Rifampicin resistant TB were included. The majority of the patients were males (65.5%) and remaining were females (34.5%). Majority patients within the age group of 18-30 year with mean age 42.42±16.37 years. Out of 113 patients, 45 (39.8%) patients were having the past history of TB. 88.5% patients had Pulmonary TB while only 11.5%patients had Extra pulmonary TB. Out of 13 Extra pulmonary TB patients, 7 (53.9%) patients had TB Lymph node followed by 4 (30.8%) patients had Pleural effusion and 2 (15.4%) patients had Abdominal Koch's. 22 (19.5%) patients had addiction of smoking followed by addiction of both alcohol and smoking in 12 (10.6%) patients. 8 (7.0%) patients had alcohol addiction. 59 (52.2%) patients had no co-morbidities while in other patients, 26 (23.0%) patients had type 2 DM followed by HIV in 17(15.0%) of patients and rest 11(9.7%) patients had both Type 2 DM & HIV. 83 (73.4%) patients had only Rifampicin resistance while the rest 30 (26.5%) patients had both Rifampicin and Isoniazid(Kat G) Resistance in First line LPA. 90 patients (79.6%) had developed adverse drug reactions during the course of treatment while the rest 23(20.4%) patients had no adverse drug reactions. 39 patients experienced only 1 ADR while the 51 patients had developed ≥ 2 ADRs

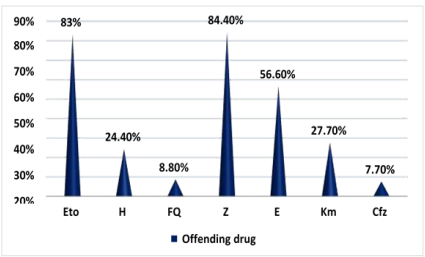
ADR	Number of Patients (n=90)	Percent (%)
GIupset (Diarrhea/nausea/vomiting)	51	56.6%
Hepatic	19	21.1%
Arthralgia	20	22.2%
Ototoxic	17	18.8%
Optic neuritis	2	2.2%
Peripheral neuropathy	5	5.5%
Dermatological	8	8.8%
Headache	8	8.8%
Hypothyroidism	6	6.6%
Nephrotic	6	6.6%
Psychiatric	5	5.5%

In our study, 90 patients experienced adverse drug reactions. 39 patients experienced only 1 ADR while 51 patients had developed > 2 ADRs. The most common adverse drug reaction was GI upset due to uncontrolled diarrhea, nausea or vomiting ,which was detected in 51 (56.6%) patients followed by Arthralgic, Hepatic and Ototoxic symptoms in 20 (22.2%), 19 (21.1%) and 17 (18.8%) patients respectively. Dermatological reactions and Headache occurred in 8 (8.8%) patients for each while Hypothyroidism and Nephrotic reactions in 6 (6.6%) patients for each. Psychiatric symptoms were observed in 5 (5.5%)patients which included depression, anxiety, nightmares and psychotic symptoms. Optic neuritis was seen in 2(2.2%) patients only.70(61.9%) patients had mild ADR while 13 (11.5%) patients had moderate ADR and 7 (6.2%) patients suffered from severe ADR.



Adverse Drug Reactions	OFFENDING DRUG INVOLVED
GI upset (Diarrhoea/nausea/vomiting)	Eto, Z,H,E
Hepatotoxicity	Eto, Z,H
Arthralgia	Z,FQ
Peripheral Neuropathy	H,Km,FQ,
Ototoxicity	Km
Skin reaction	Any drug can be involved (mainly Cfz)
Headache	Z,Eto
Hypothyroidism	Eto
Nephrotoxicity	Km
Psychiatric Symptoms	H,FQ
Optic neuritis	E,Eto

In our study, 46 (51.11%) patients had ADR within 1st month followed by after 2 months in 33 (36.6%) patients while 4(4.4%) patients suffered from ADR after 4 months. About 3 (3.3%) patients showed ADR after 5 months and 4(4.4%) patients had ADR after ≥ 6 months. The most common offending drugs were Pyrazinamide in 76 (84.4%) patients and Ethionamide in 75 (83.3%) patients followed by Ethambutol in 51(56.6%) patients and Kanamycin in 25 (27.7%) patients. Fluroquinolones were the offending drug in 8 (8.8%) patients while Clofazimine was involved in 7 (7.7%) patients.



Drug compliance was seen in 18 (20%) patients while in 65 (72.2%) patients, the offending drugs had to be stopped temporarily and in 7 (7.7%) patients had to be stopped permanently. 70 (83%) patients had sputum conversion to negative by the end of IP phase, only rest 14 (16.6%) patients had positive smear microscopy and culture by the end of IP phase. By the end of 6th month of treatment only 5 (6.5%) patients had positive smear microscopy and culture report and they were reported as treatment failure. In our study, out of 113 patients, 47 (41.5%) patients had significant improvement in clinical symptoms at the end of 1st month of treatment while the rest 66 (58.4%) patients had no significant improvement in their clinical symptoms. At the end of IP phase, only 22(23.4%) patients were symptomatic. At the end of 6th month, significant improvement in clinical findings were observed in 80 (93%) patients.

Outcome	Number of Patients (n=113)	Percent (%)
Cured	61	54%
Expired	5	4.4%
Loss to follow up	7	6.2%
On AKT	17	15%
Shifted to all oral longer	18	15.9%
Treatment failure	5	4.4%

At the end of the study, Out of 113 patients, 61(54%) patients were cured, 17(15%) patients were on treatment at the end of the study, 18(15.9%) patients were shifted to all oral longer regimen, 5 (4.4%) patients had treatment failure, 5(4.4%) patients expired and 7 (6.2%) patients were lost to follow up.

DISCUSSION

India has been identified as High-burden country of drug resistant TB. MDR TB and XDR-TB are difficult to treat day by day as it requires prolong treatment with less efficacy and high toxic drugs. ADRs associated with these drugs further complicate the picture, resulting in defaulters, insufficient treatment and thereby affect success rate. The management of ADR as well as the cost of treating ADRS is an essential component and needs to be addressed.

- Our study comprises 113 patients, in which 65.5% were males and 34.5% were females. Consistent male predominance was seen in other studies done by Vishakha K. Kapadiya and Rohan Hire. Majority of the patients (30.1%) belong to young age group (18-30 years). Vishakha K Kapadiya reported mean age was 34±11.54 years (range, 16 to 70 years). In our study, about 40.0% patients already suffered from TB in the past. Arif Dela reported out of 125 patients majority of the patients had pulmonary TB (88.5%) while only 11.5% patients
- past history of TB was present in 120 (96%) patients. Our study shows that had extra-pulmonary TB out of which 6.2% patients had cervical lymph node, 3.5% patients had pleural effusion and rest 1.8% patients were suffering abdominal koch's. Prasanta Das et al study reported that out of 203 cases, 189 (93.1%) patients were pulmonary and 14 (6.8%) patients were extrapulmonary cases. Of the 14 extrapulmonary cases, 6 were cases of tubercular lymphadenopathy and 8 patients were having pleural effusion
- In our study, Most common adverse drug reaction was GI upset in 45.0% patients followed by arthralgic, hepatic and ototoxic symptoms in 17.1%, 16.8% and 15.0% patients respectively. Dermatological reactions and headache occurred in 7.0% patients for each while hypothyroidism and nephrotic reactions in 5.3% patients for each. Psychiatric symptoms were seen in 4.4% patients while optic neuritis was seen in 1.8% patients only.
- Rohan Hire et al found that total 64 ADRs were reported in 55 patients. Gastrointestinal symptoms like nausea and vomiting contributed to 30% of total ADRs. Other ADRs includes arthralgia (4.5%), psychosis (4.5%), hepatotoxicity (3.6%), rash (3.6%), peripheral neuropathy (2.7%), renal impairment (2.7%), menstrual irregularities (1.8%), vertigo (1.8%), visual disturbances (0.9%), tendinitis (0.9%), hypothyroidism (0.9%).
- In a study by Arif Dela et al, total 147 ADRs were reported among 72 cases. gastrointestinal (GI) (24.5%) followed by weakness (21.23%), psychological (14.38%), joint pain (14.38%), and respiratory (7.8%). Less frequently reported ADRs were ototoxicity (4.1%), blurring of vision (4.1%), headache (4.1%), hepatotoxicity (2.04%), and nephrotoxicity (0.6%).

- In our study, 61.9% patients had mild ADR while 11.5% patients had moderate ADR and 6.2% patients suffered from severe ADR. A study by Rohan Hire et al reported that there were 13 mild ADR (level 1 and 2), 33 severe ADR in Level 3 and 9 ADR in Level 4 by using Hartwig's severity assessment scale. According to a study by Arif Dela et al, 77.3% ADRs were mild to moderate while 22.7% cases were severe ADR reported in his study.
- In our study, majority patients (40.7%) had ADR within 1st month followed by after 2 months in 29.2% patients while 3.5% patients suffered from ADR after 4 months. About 3.0% patients showed ADR after 5 months and 4 patients had ADR after ≥ 6 months.
- In present study, Most common offending drugs were Pyrazinamide (67.32%) and Ethionamide (66.4%) followed by Ethambutol in 45.0% and Kanamycin in 22.0% patients. According to a study by V. K. Dhingra et al., One-third patients had side-effects to ATT which required withdrawal of the offending drug. The most commonly implicated drugs were aminoglycosides (seen in four patients), followed by ethionamide, fluoroquinolones and pyrazinamide (in two patients each) and isoniazid, thiacetazone and cycloserine in one patient each.
- In our study, out of 18 patients, main cause of changing regimen was resistance to drugs while in 39.0% patients was ADR. In present study, in 3(27.2%) patients, regimen was changed to all oral longer regimen due to resistance to FQ followed by SLI (Km), Ethambutol and Pyrazinamide in 2(18.2%) patients.
- More than 80.0% of patients found negative on smear microscopy and culture report at the end of IP, at the end of 6th month and at end of treatment. According to a study by Rohan Hire et al, maximum sputum smear conversion occurred at the end of the fourth month (42.7 %) and fifth month (37.3 %) while five patients took more than six months for the same in his study.
- In our study, out of 113 patients, 47 (41.5%) patients had significant improvement in clinical symptoms at the end of 1st month of treatment. At the end of 6th month, significant improvement in clinical findings were observed in 80 (93%) patients.
- More than half of the patients were cured while 16.0% patients were shifted to all oral longer and 15.0% patients were still on AKT. About 6.0% patients lost to follow up while 4.4% patients expired during treatment. Treatment failure was seen in 4.4% patients. Vishakha K Kapadiya et al reported that forty-six patients (45.09%) were cured/treatment completed, nine patients (8.82%) failed, 21 patients (20.05%) defaulted and 26 patients (25.49%) died of total 102 patients. Treatment outcome in a study by Arif Dela et al was: cured (47.2%), transferred out (5.6%), progress to XDR (10.4%), Defaulters (13.6%) and death (22.8%).

CONCLUSION

Prevention of ADRs is always more effective than intervening after the ADRs have occurred. Hence, only vigilance about known and unknown ADRs, assessment of their causality and prompt management can mitigate toxicity. The frequency and severity of known ADRs can be reduced by monitoring laboratory and clinical parameters and instituting appropriate measures. This may help improving the compliance and ultimately quality of patient care. Thus, close monitoring and timely management are essential for treatment adherence and finally to improve outcome in MDR-TB.

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