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Study of Adverse Drug Reactions and Treatment Outcome in Patients Undergoing Multi Drug Resistance Tuberculosis

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ABSTRACT

To study of adverse drug reactions and treatment outcome in patients under shorter coarse MDR treatment. Study was conducted on 66 patients who were sputum CBNNAT positive and RIF resistant, till all the subject's treatment was completed and all the adverse drug reactions of the patient during the treatment coarse and what is the final outcome. The mean age of all 66 patients is 41±14 with most common age group of patients were in between 20-39 years. Males are more in number. Agriculture workers (42%) and daily wage labourers (39%) are most common occupational group in this study. The most common comorbid condition of the subjects in this study is Diabetes mellitus. Majority were from rural areas. Most of the patients had bmi of <18.5. Almost 26% of the patients were anaemic. The most common Chest X-ray finding among study participants is cavitatory disease (39%), B/L diffuse infiltrates (39%). Mostly lesions were located on the right side. Adverse drug reactions observed in the patients were mostly in 20-39 age group and mostly in males occurring in first three months of initiation of treatment. Adverse drug reactions were mostly observed in subjects with comorbidities, and with addictions. Gi related adverse reactions were common and were easily managed by supportive management like adding proton pump inhibitors. On grading the adverse drug reactions by using Modified Hartwig and Siegel Scale. Majority of the adverse drug reactions were graded in moderate level 4a. As per Naranjo causality assessment Scale majority of the adverse drug reactions were probable ADR'S. Out of 66 patients 67% had favourable outcome and 32% had unfavourable outcome.

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Key Words

Adverse drug reactions, multi drug resistance tuberculosis, diffuse infiltrates cavitatory disease, siegel scale

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INTRODUCTION

Till the year 2019 in Worldwide population, Tuberculosis continued to be the most important cause of death[1]. Due to rise in the global incidence of TB and the development of drug resistance. In 1.5 million people expired due to TB in 2020 (which includes 2.14 lakh people with HIV)[2]. Thirty TB-burden nations accounted for 86 percent of new TB infections in 2020. account for two-thirds of the total world TB population, of all the TB burden countries India majority of the cases are from India The present Tuberculosis diagnostic procedures are time-consuming and have inconsistent sensitivity and specificity. This results in increased mortality, morbidity and the development of drug resistance (MDR, XDR) in TB patients[3,4]. Tuberculosis (TB) is cause of death in close to 5 lakhs Indians every year[5]. a million cases go unnoticed annually either by being undiagnosed or inadequately diagnosed[6]. Drug-resistant TB is a big challenge for TB control. Resistance to anti-tuberculosis drugs can be either[7].

- **Primary,** means which is present before starting treatment due to transmission of a *M. tuberculosis* strain that is drug resistant, or
- **Secondary,** means resistance developing after start of anti tuberculosis therapy.

People Can Get Drug-Resistant Mycobacterium TB in Certain Epidemiological Situations If[8]:

Contact with a person who has drug-resistant tuberculosis.

- If Contacted with an active tuberculosis patient who failed or relapsed after receiving anti tuberculosis treatment and the patient's susceptibility test results are not known.
- Persons with active tuberculosis from places where a greater number of treatment resistance is exposed.
- Person who has sputum smear positive even after 2 months of combination treatment.
- Travel to a place where medication resistance is common.
- "It is to be noted that R resistance is quite rare without H resistance. The majority of DST findings that show R resistance will also show H resistance, indicating MDR TB. According to the National Drug Resistance Survey, (2014-16)[9].
- As a result, RNTCP to treat patients with any R resistance made a programmatic decision treating them as if they are MDR TB patients, in accordance with WHO worldwide PMDT recommendations. So MDR TB and RR TB cases are frequently grouped together as MDR/RR TB."
- A standardized treatment regimen of 12 months period was introduced by WHO for managing selected MDR-TB/RRTB patients in may 2016 this was considered as shorter MDR-TB regimen which was useful to many of MDR-TB/RRTB patients worldwide who had been following a longer regimen lasting for 18 or more months. RNTCP in 2018 introduced this the shorter MDR TB regimen in India to combat MDR-TB/RRTB cases in the country.

MATERIALS AND METHODS

Study Design:

- Prospective study, observational study.

Study Participants:

- Department of pulmonary medicine and District TB centre.

Period of Study:

- 22 months.

Inclusion Criteria:

- Patients diagnosed resistant to rifampicin in CBNNAT (pulmonary and extra pulmonary TB).
- Microbiologically confirmed resistant bacteria for two 1st line drugs (rifampicin or both inh and rifampicin).
- DST showing presence of katG mutation for H resistance.

Exclusion Criteria:

- Drug sensitive TB.
- Extremely drug resistant TB.
- DST/DRT result for FQ or SLI is resistant.
- Presence of InhA mutation in DST for H resistance.

Study Procedure:

- Patients diagnosed TB positive and rifampicin resistance by CBNNAT are considered.
- Their age, gender, chest x-ray, HIV testing were noted along with them Patients with rifampicin resistance in CBNNAT are subjected to FL-LPA, SL-LPA, DST to rule-out resistance to other anti tuberculosis drugs.
- 1. Complete Blood Count 2. B. Urea and S. Creatinine 3. Audiometry 4. Liver Function Tests 5. Thyroid Stimulating Hormone levels to assess the thyroid function 6. Urine examination-Routine and Microscopic 7. Psychiatric evaluation if required 8. Serum electrolytes 9. S. protein 10.ECG 11. Ophthalmologist opinion if required to rule out uveitis.
- Consent was taken from all patients who are initiated on shorter coarse regimen.
- The first dose is given under supervision at the treatment initiating centre for mobile patients.
- In admitted patients After discharge, the patient will be given a maximum 7 days of drug supply.
- They were followed for a period of 9-11 months (till the completion of the course).

- During this period presence of any adverse drug reactions were noted and treatment given to the patient for the adverse drug reaction was noted from dots providers and patients and severity and probability of adverse drug reactions were documented using.
- naranjo's probability assessment scale88: In the scale 10 questions were asked to which answers were 'Yes', 'No' or 'Do not Know' and after totalling the points, they were categorised into definite if 9 were yes, probable (5-8 were yes), possible (1-4 yes) and unlikely (0).
- Modified Hartwig's and Seigel scale 87 was used for understanding the severity of the ADRs where 7 questions were asked to which the answers were yes, no and don't know mild was level 1 and 2, moderate was level 3 and 4, severe was 5,6 and 7.
- At the end of course outcome of the regimen was noted.
- The data has been entered into MS-Excel and statistical analysis has been done by using MS-EXCEL. For categorical variables, the data values are represented as numbers and percentages. continuous variables, the data values are shown as mean and standard deviation.

RESULTS AND DISCUSSIONS

- The most common age group of patients in this study was 20-40 years (40.91%), followed by 40-60 years (39.39%), >=60 years (12.12%). The least common age group is >20 years (7.58%).
- With mean age of 41±14 years and median age of 40 years.

In this study, out of 66 subject's majority ie. 50 (75.76%) individuals are males and the remaining 16 (24.24%) are females. Most common age group in males is 40-60 years (23 patients out of 50) followed by 20-40 years the least common group is <20 yrs age group (1 patient out of 50). in females most common age group is 20-40 years 9 followed by <20 years 4 patients in 40-60 yrs. age group there are 3. Out of 66 cases 39 (59.1%) reported from rural areas and 27 (40.9%) reported from urban areas. Out of 66 cases 32 (58%) patients Body mass index was >18.5 and 34 (52%) patients were <18.5. In this study contact with TB confirmed patient was observed in 64 (97%) patients. 3 (4.55%) subjects out of 66 subjects had previous PTB history and used att for 6 months period majority were from agricultural sector i.e., 28 patients (42.42%) followed by daily wagers who were 26 patients (39.39%), 3 (4.55%) were doing private jobs, 5 (7.58%) patients were housewives and 4(6.06%) were students. In the study, out of 66 patients, 23(34.85%) patients had h/o smoking and 11 (16.67%) had a history of alcohol intake and 12 (18.18%) had a history of tobacco chewing. Among the patients in the study, the most common comorbid condition is diabetes mellitus 13 patients in the study had diabetes mellitus followed by COPD which was observed in 10 patients, Hypertension seen in 9 patients, Asthma seen in 3 patients and CKD seen in1 patient. Chest x ray findings in our study are 26 cases (39.39%) of the cases show b/l infiltrate changes 26 cases (39.39%) show cavitatory lesion on chest x ray 13 cases show consolidators changes on chest x ray and 1 case show pleural effusion findings on chest x ray. Out of 66 patients 9 (13.64%) were reactive to HIV and 57 (86.36%) were non reactive. Out of 66 subjects in the study 17 subjects had anaemia during the time of diagnosis and before initiation of treatment. in this study most of the individuals who were initiated on short coarse MDR majority of them were under weight band of 46-70 kg group followed by 30-45 kg wt band, 16-29kg band and >70kg band group. In age wise distribution of adverse drug reactions adverse drug reactions were mostly noted in age group of 20-39 years involving 38 out of 83 adverse events followed by 40-59 years age group involving 30 adverse events. There were total of 83 adverse drug reactions noted in the study population through out the treatment period of which majority of ADR were seen in males. males in the study developed a total of 48 adverse events and females developed 35 adverse events in the 9 months treatment period most common adverse events in both male and female are gastric related involving gastritis of 19 adverse events followed by nausea and vomiting involving 13 adverse events. Out of nine hiv reactive patients 8 patients (88.89%) had adverse drug events of which majority had 3 or more adverse reactions during the treatment period. And in 57 non-reactive patients 38 (66.67%) had adverse drug reactions of them majority had single adverse drug reaction during treatment period. Probability of each ADR (n=83) were graded according to Naranjo's Scale84 9 were identified as definite ADR'S, 39 ADRs as "Probable" ADRs and 37 ADRs as "Possible" ADRs. According to Modified Hartwig and Seigel severity scale, out of 83 ADRs, 17 were graded into mild level 1 ADRs, 21 were graded as mild level 2 ADRs., 8 were grade as moderate level 3 ADRs, 30 as moderate level 4 ADRs., 4 were graded as severe level 5 ADRs and 2 were graded as severe level 6 ADRs. and 1 was grades as severe level 7 ADR.

Table 1. Occurrence of Adverse Drug Reactions After Initiation of Treatment

Adverse drug events	First 4 months	4–8 months	8-11 months
Peripheral neuropathy	6	1	0
Giddiness	8	3	0
Nausea and vomiting	6	5	2
Gastritis	12	3	2
Dermatitis	10	3	0
Hepatotoxicity	8	3	1
Nephrotoxicity	1	2	0
Visual Impairment	1	2	1
Ototoxicity	1	2	0
Adverse drug events	53	24	6

The most common adverse effect reported by the end of the 4th month was GASTRITIS, followed by other common side effects including dermatitis,

hepatotoxicity, giddiness, peripheral neuropathy and mild hearing loss. The most common side effect reported by the end of the 7TH month was nausea and vomiting, followed by other common side effects including gastritis, hepatotoxicity, giddiness, blurring of vision, ototoxicity and nephrotoxicity from 8th month till the end of treatment most common adverse effects reported were nausea and vomiting followed by severe gastritis, visual impairment and hepatotoxicity.

Table 2. Treatment Outcome in the Case Study

Outcomes	Frequency	Percentage
Cured	38	57.58%
Treatment Completed	7	10.61%
Treatment Failed	0	0.00%
Died	8	12.12%
Lost to Follow Up	10	15.15%
Regimen Changed	3	4.55%

Out of 66 cases in the study 45 (38 (57.38%) are cured cases and 7 (10.61%) treatment is completed) cases had favourable out come and 21 cases (8 (10.71%) died 10 (10.71%) lost to follow up and 3 (4.55%) cases were changed to all oral longer regimen) had un favourable out come.

Most of the males are from 40-59 age group and most of the females are from 20-39 age group. Adverse drug reactions were frequently seen in 20-39 years age group followed by 40-59 years and <20 years similar to studies by Trubnikov[10]. Majority of the subjects are from rural areas. out of 66 39 (59.1%) were residing in rural areas and 28 (40.9%) are from urban areas. <Half of study patients were under weight (51.51%). This supports malnutrition as a risk-factor for TB. Was similar to other study by A. Tre ´bucq[11] (<18.5= 56.4%). Majority of the HIV patients developed adverse effects of short course MDR regimen. Three of them expired during intensive phase of treatment itself. Three of them had lost to follow up due to adverse drug reactions. But 3 completed full course of short course regimen inspite of developing adverse effects of drugs. OUT OF 66, 39 (59.09%) subjects had one or more comorbidities and most common comorbid condition is diabetes mellitus (19.70%), followed by COPD (15.15%), Hypertension (13.64%), Asthma and CKD (1.43%). In a study by Aleksandr Trubnikov *et al* (N=95) 56 (58.9%) patients had comorbidities which is similar to our study. Adverse events and poor outcomes are more common in patients with comorbidities than in people without comorbidities. This is not only due to presence of comorbid conditions but also due to multiple drug interactions by medication used in those conditions. Chest radiograph plays an important role in the management of TB. Even though it cannot confirm, it can give initial clues and also crucial for follow up. There were 4 different radiological findings commonly observed in chest radiographs of study subjects. They were bilateral diffuse infiltrates, consolidation, cavities and pleural effusion. 26 (39%) had bilateral infiltrates, 26 (39%) had cavitatory lesions followed by consolidation in 13 (20%). Only 1 patient had pleural effusion (a case of with pleural fluid DR-TB). Adverse drug reactions are common causes for decreased adherence to MDR-TB treatment. 46 (69.6%) developed at-least one adverse drug reaction during treatment requiring either addition of a supportive treatment or with-holding of offending medication. similar findings were also mentioned by Törün[12] (69.2%). But some other studies by Mayur P. Shinde[13], 60 (12.82%). Most of the adverse reactions were observed in the first 4 months of treatment.

In Our Study Out of 83 ADRs:

- 38 (47%) were classified as “Mild” ADRs.

In them 17 were from level 1 and 21 were from level 2

- 38 (47%) were classified as “moderate” ADRs In them 8 were from 3, 30 were from level 4.
- 7 (8.4%) were classified as “severe” ADRs.

In them 3 from level 5, 3 from level 6 and 1 from level 7. In a study by Leya P. Babu[14] majority of the ADR were moderate level 4b and followed by mild level 2, which is similar to our study. ADRs were managed symptomatically. In severe conditions, the offending medication was either changed or completely stopped. For gastritis proton pump inhibitors were used. For skin adverse effects such as dermatitis, initially antihistamines were given. But for 2 people, the offending drugs Eto and Lfx were replaced with PAS.

For peripheral neuropathy T. pyridoxine 100 mg was given 6 days in a week and in one patient holding of Eto was required. For nephrotoxicity, injectable agents were stopped in 2 patients as their creatinine levels continued to rise despite with twice/thrice week dosing, and was replaced with PAS. rest of the treatment was continued in the same way. Out of 2, one patient even after replacing the drug s. Creatinin levels were increasing hence needed hemodialysis during treatment period. 3 patients had ototoxicity. Of which one had vertigo and was treated with oral tablet betahistin 8mg/ tid,1 had Tinnitus and mild hearing loss so dose of Km was reduced. one had permanent hearing loss even after stopping Km. In 2 patients with visual impairment offending drug lzd and ethambutol were stopped. and patient was referred to an ophthalmologist. Total 45 (68.18%) patients could complete full course of MDR-TB regimen. 38 (57.57%) were cured. But it was different in previous studies which had relatively high cured rate by K. J. M. Aung[15] 21 (31.81%) cases could’nt complete full course of treatment and had poor outcome. 8 (12.12%) died during treatment, 10(15.15%) lost to follow up, 3(4.54%) required change of regimen to all oral longterm regimen. Subjects with low body mass index (BMI), comorbidities (HTN, DM, COPD, CKD) and other risk factors (smoking, tobacco-chewing, alcohol consumption) had poor treatment outcome.

CONCLUSION

The following conclusions were made by the study. Common ADR'S were of more frequently reported in males. OF all ADR'S GI related adverse effects were more common compared to the rest. Most of ADRs were of moderate severity and had a probable relationship with the suspected drugs. Most of the ADR'S were manageable symptomatically except for few adverse effects like ototoxicity, hepatotoxicity and nephrotoxicity in one or two cases needed change in therapy like temporary witholding the offending drug and restarting it in the later course of treatment. One needed discontinuation of the offending medication. Subjects taking ART along with this shorter MDR regimen had more frequency of adverse reactions. Outcomes were good in majority of the patients. So close monitoring of patients, watching for ADR's during the course of treatment can reduce drug toxicity due to MDR-TB regimen and also improves patient's compliance with the regimen.

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