

## **A study on treatment outcome and adverse drug reactions among extra pulmonary tuberculosis patients treated under DOTS in a tertiary care hospital**

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### **ABSTRACT**

**Background:** Pulmonary tuberculosis being the predominant manifestation of the disease Extra-Pulmonary sites can also involve as a result of dissemination from a chief focus. The present study aims to determine the presentation and outcome of patients with extra-pulmonary tuberculosis treated with category I DOTS and to identify the incidence and pattern of ADRs caused by anti-tubercular drugs and to assess the causality and severity of the reported ADRs.

**Methods:** Data was collected from cases of Tuberculosis patients diagnosed and treated under category I DOTS at Sri Siddhartha Medical College for the period of one year (during 2015). These patients were monitored for ADRs during OPDs and hospital stay. Any Adverse effects observed were recorded in 'Adverse Drug Event Reporting Form' prepared by the CDSCO, Govt. of India. The data were evaluated for patient demography, types of TB, incidence of ADRs, onset and outcome of the ADRs. ADRs were also assessed for their causality and severity by using WHO-UMC criteria and Hartwig's scale.

**Results:** Extra-pulmonary cases accounted for 32.2% of total TB cases. Among 224 cases of extra-pulmonary TB studied, 136 (60.7%) were males and 88 (39.3%) were females. Among these patients 82.2% completed treatment, 7.5% were defaulted, 9.9% died and 0.4% treatment failure. The most common reason for default was irregular treatment (29.5%) followed by alcohol abuse (23.5%). Among 224 patients of EPTB who were started on ATT as per DOTS, we noted ADR in 52 patients and 73 ADRs. Gastritis was the most common ADR (25%) followed by anorexia (14%) and skin reactions (9.6%) and multiple drug therapy was the major predisposing factor for these ADR's.

**Conclusions:** Extra-pulmonary Tuberculosis accounts for 32.2% of the total cases studied. Treatment irregularities and alcohol abuse are the two most common reasons for default. On evaluation of the causality of ADRs, majority of them were found to be 'possible' by WHO-UMC and Naronjo's causality assessment scale. The severity assessment of ADRs showed that 42% reactions were moderate and 58% were of the 'mild' nature.

**Keywords:** ATT - antitubercular drugs, ADR - Adverse drug reactuins, DOTS - Directly Observed Treatment Short-course, Extra-pulmonary Tuberculosis, Hartwig's scale, Naronjo's causality assessment scale, World Health Organization -Uppsala monitoring centre (WHO-UMC)

### **INTRODUCTION**

Tuberculosis is primarily a disease of the lungs but can affect almost any organ in the body. The term extra-pulmonary tuberculosis is referred to describe the occurrence of TB at sites other than the lung. The most common sites of extra-pulmonary tuberculosis are lymph nodes, genitourinary tract, pleura, bones and joints,

meninges and the central nervous system, peritoneum and other abdominal organs.<sup>1</sup> Tuberculosis also exists in a disseminated (miliary) form, with a general bacteraemia spreading the infection throughout the body.<sup>2</sup>

In 2014, there were an estimated 9.6 million incident cases of TB (range, 9.1 million-10.0 million) globally, equivalent to 133 cases per lakh population. The absolute

number of incident cases is falling slowly, at an average rate of 1.5% per year 2000-2014 and 2.1% between 2013 and 2014. The cumulative reduction in the TB incidence rate from 2000-2014 was 18%. Most of the estimated number of cases in 2014 occurred in Asia (58%) and the African Region (28%); smaller proportions of cases occurred in the Eastern Mediterranean Region (8%), the European Region (3%) and America (3%). The six countries that stand out as having the largest number of incident cases in 2014 were India, Indonesia, China, Nigeria, Pakistan and South Africa. India, Indonesia and China alone accounted for a combined total of 43% of global cases in 2014.<sup>3</sup>

Although pulmonary tuberculosis is the most common presentation of tuberculosis disease, it can involve any organ in the body. Extra pulmonary Tuberculosis (EPTB) is defined as the isolated occurrence of TB in any part of the body other than lungs. Mycobacteria may spread to any organ of the body through lymphatic or haematogenous dissemination and lie dormant for years at a particular site before causing disease. Manifestations may relate to the system involved, or simply as prolonged fever and nonspecific systemic symptoms. Hence diagnosis may be elusive and is usually delayed. The proportion of EPTB among all TB cases varies from country to country. The extra-pulmonary manifestation of TB is prevalent in 10-34% of non-HIV cases while it occurs in 50-70% of patients co-infected with HIV. Tuberculous lymphadenitis is the most common form of extra-pulmonary tuberculosis and cervical lymph nodes are most frequently involved group among peripheral lymph nodes.<sup>4</sup>

The currently indorsed anti-tuberculosis regimens are usually well tolerated. However some patients may experience problems, usually due to the bulk of the drugs, a single day's dose consisting of more than five drugs. Drug related side effects might be minor or major.<sup>5</sup> In general, a patient who has minor side effects should be encouraged to continue the treatment with symptomatic measures such as antacids, antihistamines, antiemetics, or analgesic. If major side effects occur, the regimen or the offending drug, if identified, must be stopped. Further management depends on the nature of side effects and may have to be done in a hospital.<sup>6</sup> Antitubercular drugs, just like other drugs used in clinical practice, is not free from side effects. The added problem is that combinations of drugs are always used for prolonged periods of time<sup>7</sup> and therefore, it is likely that the adverse reactions of one drug may be potentiated by the companion drugs used. Hence, there is a need to monitor the side effects of antitubercular drugs in a hospital set up.

## METHODS

Data was collected from cases of extra-pulmonary TB diagnosed in Sri Siddhartha Medical College Hospital and Research centre, Tumakuru in the year 2015 that are

treated under directly observed short course chemotherapy (DOTS). Demography of these patients was noted and extra pulmonary site of infection were recorded in order. Treatment outcome was evaluated as cured, completed treatment, defaulted, failed, or died based on the definitions given by the WHO. Inclusion Criteria for this study includes all cases of extra-pulmonary TB of all age groups and both sexes treated at our centre by DOTS. Exclusion Criteria includes any cases of pulmonary TB, DM, IHD, CKD and HIV co-infection, cat II ATT and patients with previous history of allergy to anti-tubercular drugs.

All the patients of tuberculosis were enrolled after taking their informed consent and monitored for ADRs. Patient profile was maintained to identify the patient demography, date of start and completion of treatment, record of follow-up, types of EPTB and incidence of ADRs, onset, management and outcome of the ADRs. Any adverse effects observed were recorded in the 'Adverse Drug Event Reporting Form' prepared by the CDSCO, Govt. of India. ADRs were also assessed for their causality and severity as per the standard algorithms. 224 cases were studied for ADR monitoring during the study period and causality was assessed using world Health Organization - Uppsala monitoring centre (WHO-UMC) and Naronjo's causality assessment scale. Severity was assessed by Hartwig's questionnaire.

The study was conducted after obtaining ethical clearance from institutional ethical committee. The statistical analysis was done by using descriptive analysis.

## RESULTS

Overall 2145 suspected cases of tuberculosis were analyzed at our site during the year 2015. Among them 752 cases of TB diagnosed. They are further classified as Sputum Positive Pulmonary TB (n=456), Sputum Negative pulmonary TB (n= 53) and Extra-pulmonary TB (n=243). Extra-pulmonary cases accounted for 32.2% of total TB cases (Table 1).

**Table 1: Total number of pulmonary and extra-pulmonary cases.**

Total number of cases of pulmonary TB			
Total number of TB suspected cases	Number of sputum positive cases	Number of x-ray positive, smear negative cases	Total number of Extra-pulmonary cases diagnosed
2145	456 (60.6%)	53 (7.04%)	243 (32.2%)

After inclusion and exclusion criteria 224 cases of extra-pulmonary TB cases were included in the study. Among them 136 (60.7%) were males and 88 (39.3%) were females and most of the patients were in the age group of

21-40 years (Table 2). In our study of 224 cases of extra-pulmonary tuberculosis, most common site of extra-pulmonary tuberculosis was pleura (29.9%) followed by meninges (22.5%), abdomen (19.6%) and Lymph node (10.7%) tuberculosis. The least common sites were hip joint, elbow joint, omental mass, skin TB and miliary TB (Table 3).

**Table 2: Age and Sex distribution of cases.**

Age	Sex		Total
	Male	Female	
<20 years	23	31	54
21-40 years	79	39	118
41-60 years	26	14	40
>60 years	08	04	12
Total	136 (60.7%)	88 (39.3%)	224

**Table 3: Sites of extra-pulmonary tuberculosis.**

Sr. No.	Sites of extra-pulmonary tuberculosis	Number of patients	Percentage (%)
1	Pleura	67	(29.9%)
2	Meninges	51	(22.5%)
3	Abdomen	44	(19.6%)
4	Lymph node	24	(10.7%)
5	Spine	11	(4.9%)
6	Tuberculoma	11	(4.9%)
7	Eye	03	(1.3%)
8	TB osteomyelitis	03	(1.3%)
9	Knee joint	03	(1.3%)
10	Ileocaecal	02	(0.8%)
11	Hip joint	01	(0.5%)
12	Elbow joint	01	(0.5%)
13	Omental mass	01	(0.5%)
14	Skin TB	01	(0.5%)
15	Miliary TB	01	(0.5%)
Total		224	(100%)

Among 224 cases of extra-pulmonary tuberculosis who are on DOTS treatment, 184 (82.2%) patients completed treatment, 17 (7.5%) patients defaulted, 22 (9.9%) patients died and there was 01 (0.4%) case of treatment failure (Table 4). Out of 17 defaulters, the most common reason for defaulting treatment was irregular treatment (29.5%) and alcohol abuse (23.5%) none was due to ADR (Table 5).

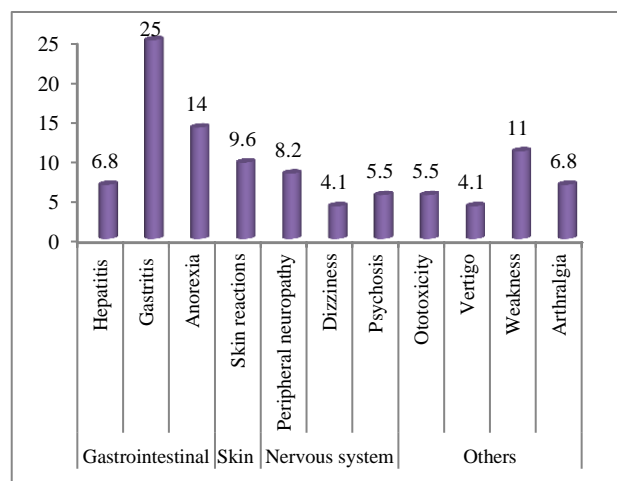
**Table 4: Treatment outcome of total subjects.**

Treatment outcome	Results (number of patients)	Percentage (%)
Treatment completed	184	(82.2%)
Defaulted	17	(7.5%)
Died	22	(9.9%)
Failure	01	(0.4%)
Total	224	(100%)

**Table 5: Reasons for default.**

Reason for default	Number of patients (%)
Irregular treatment	05 (29.5%)
Alcohol	04 (23.5%)
Refused DOTS drugs	02 (11.7%)
Pulmonary embolism	01 (5.8%)
Not known	05 (29.5%)
total	17 (100%)

Out of these 224 patients only 52 patients developed 73 ADRs of various types. Among the 73 reported ADRs, most were observed in males (32/61.5%) and remaining (20/39.5%) were females. The overall incidence of ADRs was 23.2%. ADRs in this study were categorized according to the systems affected like gastrointestinal system, skin, nervous system and other systems like vestibular, muscle etc. Majority of ADRs were related to gastrointestinal system (33 cases) followed by central nervous system (13 cases), skin (7cases) and other systems (20 cases). Gastritis was the most common ADR (18/25%) followed by anorexia (10/14%) and skin reaction (7=9.6%) and peripheral neuropathy (6/8.2%) and Hepatitis (5/6.8%) (Figure 1).



**Figure 1: The figure depicts the frequency of distribution of adverse drug reaction to anti tubercular drugs.**

In 87% of the cases, the suspected drug was continued in spite of the ADR, without any complications. 6 (8.2%) of the ADRs occurred on the first day of the treatment. 32 ADRs (43.8%) occurred within a week of treatment, 28 (38.3%) in the second week, 7 (9.58%) in the third week of the initiation of anti tubercular therapy. Causality evaluation studies of ADRs, revealed majority of them were found to be 'possible' (WHO-UMC and Naranjo's scales). These ADRs were classified into different levels like mild, moderate or severe based on the Modified Hartwig and Siegel scale. The severity assessment of ADRs showed that 42% reactions were moderate and 58% were of the 'mild' nature as per the Hartwig et al scale.

## DISCUSSION

We studied 2145 suspected cases of tuberculosis at our site during the year 2015. Among 752 cases of TB diagnosed, 456 had Sputum Positive Pulmonary TB, 53 had Sputum Negative pulmonary TB and 243 had Extra-pulmonary TB. Sputum positive Pulmonary TB accounted for 60.2%, Sputum negative Pulmonary TB 7% and extra-pulmonary cases accounted for 32.2% of total TB cases. Our study is consistent with study done by Chandir S.<sup>4</sup> In present study tuberculosis was seen more in males compared to females. Similar results were seen in other studies.<sup>8,9</sup> However, Mir Azam Khan reported equal number of cases in both sex.<sup>10</sup> In our study the most common site of extra-pulmonary tuberculosis was pleura followed by meninges, abdomen and lymph node. The least common sites were hip joint, elbow joint, omental mass, skin TB and miliary TB. In a study conducted in south India, among extra pulmonary tuberculosis subjects, lymph node tuberculosis was most common followed by pleural tuberculosis, tuberculosis of abdomen, meninges, hip joint and skin.<sup>11</sup>

In the present study among 224 cases of extra-pulmonary tuberculosis that were put on DOTS treatment, 184 (82.2%) patients completed treatment, 17 (7.5%) patients were defaulters, 22 (9.9%) patients died and there was 01 (0.4%) case of treatment failure. Similar study conducted by Chandir S, showed higher Default rate (34.5%) and only 59.8% patients had completed treatment and more treatment failures (5.2%) compared to our study and finally 0.5% patients died during treatment in this study.<sup>4</sup>

The most common reason for default in our study was irregular treatment (29.5%) followed by alcohol abuse (23.5%). Chandrashekar reported illiteracy, alcohol intake and smoking as the causes for default.<sup>12</sup> The study by Tekle reported that default was 11.3%, the reason being lack of family support, inadequate knowledge of treatment duration and side effects of medication.<sup>13</sup> In our study, 8 (3.6%) patients were found to be reactive for HIV antibodies and the remaining 116 patients were nonreactive. In various other studies, seroprevalence varied from 0.4%- 10.9%.

Out of 224 patients enrolled in the study, 52 patients developed 73 ADRs (23.2%). The highest numbers of ADRs (32/61.5%) were observed in males which are in contrast to the study by Yee and Shakya et al which showed female gender as a risk factor for the occurrence of ADRs due to anti-TB drugs.<sup>14</sup> But in the study, by DK. Tak et al, males developed more ADRs, which could be due to majority of males included in the study.<sup>15</sup> In our study, 172 patients were under 40 years of age (76.8%) followed by 40 resides in age of 40-60 (17.8%) and 12 were in more than 60 years age group (5.35%). This result is in contrast to the study by Yee et al where age over 60 years was associated with increased incidence of ADRs due to anti TB drugs. A study conducted by Daphne et al showed that ADRs due to anti tubercular

drugs occurred in patients above the age of 60 years.<sup>16</sup> But in our Study, majority of ADRs were observed in patients below 60 years of age this may be due to less number of patients in above 60yrs age group. We noted 71(97.2%) ADRs in less than 40 years and 40-60 years of age group. 6 (8.2%) of the ADRs occurred on the first day of the treatment. 32 ADRs (43.8%) occurred within a week of treatment, 28 (38.5%) in the second week, 7 (9.58%) in the third week of the initiation of anti tubercular therapy. The highest reported ADR was gastritis (25 %) which is in accordance to the study by Dhingra et al, where it was around 53%. Anorexia was the second common ADR noted 14% and followed by skin reactions, Peripheral neuropathy were next common ADRs observed in our study population, whose occurrence was comparable to that found in the study conducted by Dhingra et al.<sup>17</sup>

On evaluation of the causality of ADRs, a majority of them were found to be 'possible' by both WHO-UMC and Naranjo's scales. The reported ADRs were classified into different levels like mild, moderate or severe based on the Modified Hartwig and Siegel scale. The severity assessment of ADRs showed that 42% reactions were moderate and 58% were of the 'mild' nature as per the Hartwig et al scale.

## CONCLUSION

This study was conducted to study extra-pulmonary TB cases in our centre and to determine the treatment outcome of these patients treated under DOTS and also to look ADRs of ATT in these patients. Extra-pulmonary Tuberculosis accounts for 32.2% of the total cases studied. Pleura are the most common site of Extra-pulmonary TB in our study. Treatment irregularities and alcohol abuse are the two most common reasons for default. Anti tubercular drugs may cause significant reactions leading to change of therapy, prolonged hospital stay and even death. We noticed more number of ADRs in males. Gastrointestinal system was the most common system involved in ADRs of ATT and multiple drug therapy being the major predisposing factor. Most of the ADRs reported in our study were categorized as mild to moderate severity. In majority of the cases, ATT was continued in spite of the ADRs, without any complications. Proper counselling of patients regarding timely prevention, detection and timely management of ADRs needed to prevent serious complications.

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