ORIGINAL ARTICLE

TREATMENT OUTCOME AND ADVERSE EFFECTS OF DRUG RESISTANT TUBERCULOSIS PATIENTS AT LARKANA AND SUKKUR TUBERCULOSIS CENTRES

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Background: Anti-tuberculosis drug resistant is a major public health problem worldwide. It arises due to improper use of anti-tuberculous drugs in susceptible TB patients. The objectives of this study were to evaluate treatment outcomes and adverse effects of drug resistant tuberculosis patients. **Methods:** A descriptive cross-sectional study was conducted in two Programmatic Management of Drug Resistant Tuberculosis (PMDT) sites of Sukkur and Larkana. The sociodemographic data was obtained by a set of questionnaire following WHO guidelines. Adverse drug effects and treatment outcome data was gathered from their medical files. **Results:** Of a total 938 patients, 535 (57.1%) were male and 403 (42.9%) were female. Their mean age was 35.95±14.4 years in Sukkur and 35.46±11 years in Larkana. Married patients were 69%, illiterate were 46.3%, farmers 36.8%, lower class 60.4%, and rural were 68.8% patients. Previously treated cases were 83%. The MDR-TB cases were 82.8%. Diabetes mellitus as co-morbidity was 11.2%, and 41.3% were smokers. The adverse effects developed in 68.4% patients. Overall successful treatment outcome rate was 53.9%. **Conclusion:** Treatment outcome of drug resistant TB patients was quite low, and 68.4% patients developed adverse effects. Artharlgia was the most common adverse effect.
Keywords: Tuberculosis, Drug Resistant Tuberculosis, Adverse drug effects, Treatment failure

INTRODUCTION

Pakistan is ranked 5th among high burden countries worldwide which accounts 61% of the TB burden in the WHO Eastern Mediterranean region. Pakistan has an estimated 510,000 new TB cases and approximately 15,000 of them are developing drug resistant TB cases emerging every year. The drug resistant TB is a re-emerging threat worldwide as the number of cases is increasing every day.[1] Drug resistant tuberculosis, especially multi drug resistant tuberculosis cases are increasing most frequently. The World Health Organization defines the Multidrug Resistant TB (MDR-TB) as a type of TB which is resistant to both Isoniazid (INH) and Rifampicin (R). The most important anti-tuberculosis first line drugs according to the classification of TB drugs.[2−4] The MDR-TB develops due to the genetic mutation of Mycobacterium Tuberculosis because of the improper treatment with first line anti-tuberculosis drugs and most importantly non-adherence and non-compliance of patients to treatment.[1,5,6] This drug resistant TB has been always a reason of burden over the National TB Control Program (NTP).[7,8] It has been observed from several studies that reoccurrence of multi drug resistant tuberculosis after successful treatment has become a widespread observable fact. It has been reported that occurrence of MDR-TB after successful treatment is from 3.2% to 4.4% every year.[3-4] Majority of MDR-TB patient have not end up with successful treatment outcomes.[9] Some of drug resistant TB (DR-TB) patients have failed in treatment or they lost the follow-up of treatment.[10] Those retreated cases of drug resistant TB who had exposure with second line drugs are actually posing the challenges because of very close contacts with previously treated drug resistant TB patients.[11,12] The patients who are under long term treatment are facing adverse drug effects and chances of successful outcomes rates are critically low.[13]

The current study was proposed to evaluate the overall treatment outcome rate as well as adverse drug effects experienced during the long course of treatment therapy on second line drugs of drug resistant Tuberculosis patients enrolled in two Programmatic Management of Drug Resistant Tuberculosis (PMDT) sites of Larkana and Sukkur tuberculosis centres.

MATERIAL AND METHODS

This descriptive, cross-sectional study was conducted in two PMDT sites working under National TB Control Program (NTP) Pakistan, located in TB centres of Gullam Muhammad Mahar Medical College (GMMMC) Sukkur, and Chandka Medical College (CMC) Larkana respectively. All bacteriological and Drug Sensitivity Testing (DST) confirmed DR-TB patients enrolled from January 2015 to December 2017 were included in this study. The socio-demographic

characteristic and previous medical history records data was obtained from patients by interview through a well-structured questionnaire following the WHO/NTP guidelines. The data of clinical investigations, pattern of drug resistance, adverse drug reaction, and overall treatment outcomes of patients were obtained from drug resistant tuberculosis register, medical record files, and some data was extracted from Electronic Numerical Recording System (ENRS) that is a uniform format for data storage provided by WHO/NTP across all PMDT sites. Data was analyzed using SPSS-16.

RESULTS

Out of 938 confirmed DR-TB patients, 616 (65.7%) were from PMDT site Sukkur including 345 (56.0%) males and 271 (44.0%) females, whereas 322 (34.3%) were from PMDT site Larkana including 190 (59.0%) males and 132 (41.0%) females (*p*=0.209). The mean age of patients was 35.95±14.41 years in Sukkur and 35.46±11 years in Larkana TB canters (*p*=0.528).

Among socio-demographic characteristics, 68.8% patients were from rural and 31.2% from urban areas. Married patients were 69%, Single 28.2% and 2.8% were widowed/divorced. Majority (46.3%) of the patients were illiterate followed by Primary level (29.6%), Matriculation level (15.1%), Intermediate (5.3%), and 3.6% were graduates (*p*=0.006). Majority (36.8%) of patients were Farmers, followed by House-wives (30.5%), Un-employed (16.1%), Businessmen (6.6%), Government servants (3.2%), and others (6.8%).

Majority (60.4%) of patients were placed in lower socioeconomic class, 29.0% in middle class, and 10.6% were upper class (Table-1).

New drug resistant TB cases that had no exposure to anti-TB drugs before were 17%, and 83% cases had previously been treated (*p*=0.001). There were 82.8% MDR-TB patients followed by Mono resistant (6.2%), MRTB/RIF on Gxpert (5.1%), Poly resistant (4.6%), and 1.3% were XDR-TB cases. Among the DR TB patients 69.4% had no co-morbidity, 11.2% had Diabetes Mellitus, 7.5% had Chronic Obstructive Pulmonary Disease, 5.4% had Chronic Liver Disease, 3.2% had Cardio Vascular Disease, and others co-morbidities were seen in 3.3% (*p*=0.003). Ninety-five percent patients had pulmonary disease and 5% had extra-pulmonary disease. Smokers were 41.3% and non-smokers were 58.7% (*p*=0.000). HIV reactive patients were 2.6%, non-reactive were 93%, and 4.4% patients had no data of HIV (*p*=0.000). Adverse drug effects were seen in 68.4% patients whereas 31.6% patients did not experience adverse effects (Table-2).

The most common adverse effect observed amongst patients was Artharlgia in 33.0% patients followed by Gastrointestinal tract disorders (17.7%), CNS disorders (14.4%), Respiratory disorders (8.0%), Ototoxicity (6.4%), Hepatotoxicity (5.8%), Skin allergic

reactions (3.2%), and others (3.4%) produced in drug resistant patients with Second Line Drugs (Table-3).

The overall successful treatment outcome was (53.9%) which includes treatment completed (6.9%) and cured (47%); whereas unsuccessful treatment outcome was (46.1%) which includes death (1.9%), treatment failed (21.2%), lost to follow-up (21.2%) and transfer out (1.8%) (Table-4).

Table-1: Socio-demographic characteristics of Drug Resistant Tuberculosis patients [n (%)]

Characteristics	Sukkur (n=616)	Larkana (n=322)	Total (n=938)	*p*
Age (Mean±SD)	35.95±14.41	35.46±11	35.95±14.4	0.528
Gender				
Male	345 (64.5)	190 (35.5)	535 (57.1)	0.209
Female	271 (67.2)	132 (32.8)	403 (42.9)	
Marital Status				
Single	165 (26.7)	100 (31.0)	265 (28.2)	
Married	433 (70.3)	214 (66.5)	647 (69.0)	0.167
Widowed/ divorced	18 (3.0)	8 (2.5)	26 (2.8)	
Educational status				
Illiterate	261 (60.1)	173 (39.9)	434 (46.3)	
Primary Level	191 (68.7)	87 (31.3)	278 (29.6)	
Matriculation	104 (73.2)	38 (26.8)	142 (15.1)	0.006*
Intermediate	39 (78.0)	11 (22.0)	50 (5.3)	
Graduation	21 (61.8)	13 (38.2)	34 (3.6)	
Occupational status				
Govt: Servant	18 (3.0)	12 (3.7)	30 (3.2)	
Private Business	20 (3.2)	42 (13.0)	62 (6.6)	
House Wife	242 (39.3)	44 (13.7)	286 (30.5)	
Unemployed	74 (12.0)	77 (24.0)	151 (16.1)	0.000*
Farmer	233 (37.8)	112 (34.8)	345 (36.8)	
Others	29 (4.7)	35 (10.8)	64 (6.8)	
Socio-economic status				
Lower class	385 (62.5)	182 (56.5)	567 (60.4)	
Middle class	172 (28.0)	99 (31.0)	271 (29.0)	0.051
Upper class	59 (9.5)	41 (12.5)	100 (10.6)	
Locality of patients				
Rural	416 (64.5)	229 (35.5)	645 (68.8)	0.147
Urban	200 (68.3)	93 (31.7)	293 (31.2)	

*Significant

Table-2: Clinical characteristics and medical history of drug resistant TB patients [n (%)]

Characteristics	Sukkur [n=616]	Larkana [n=322]	Total [n=938]	*p*
Type of DR-TB patients				
New cases	101 (16.4)	58 (18.0)	159 (17.0)	0.001*
Previously treated cases	515 (83.6)	264 (82.0)	777 (83.0)	
Types of drug resistant TB				
Mono resistant	37 (6.0)	21 (6.25)	58 (6.2)	
Poly resistant	28 (4.5)	15 (4.7)	43 (4.6)	
MDR TB	511 (83.0)	266 (82.6)	777 (82.8)	0.012
XDR TB	8 (1.3)	4 (1.2)	12 (1.3)	
MTB/RIF on Gxpert	32 (5.2)	16 (5.0)	48 (5.1)	
Co-morbidities with DR-TB				
No co-morbidity	452 (73.4)	199 (61.8)	651 (69.4)	
COPD	44 (7.1)	26 (8.1)	70 (7.5)	
DM	58 (9.4)	47 (14.6)	105 (11.2)	0.003*
CLD	24 (3.9)	27 (8.4)	51 (5.4)	
CVD	20 (3.2)	10 (3.1)	30 (3.2)	
Others	18 (2.9)	13 (4.0)	31 (3.3)	
HIV status				
Reactive	4 (0.6)	21 (6.5)	25 (2.6)	0.000*
Non reactive	611 (99.2)	261 (81.1)	872 (93.0)	

Not record	1 (0.2)	40 (12.4)	41 (4.4)	
Smoking habit				
Smoker	194 (31.5)	193 (60.0)	387 (41.3)	0.000*
Non/ex-smoker	422 (68.5)	129 (40.0)	551 (58.7)	
Site of disease				
Pulmonary	574 (64.4)	317 (35.6)	891 (95.0)	
Extra-pulmonary	42 (89.7)	5 (10.6)	47 (5.0)	
Adverse drug effects				
Yes	411 (66.7)	231 (71.7)	642 (68.4)	0.116
No	205 (33.3)	91 (28.3)	296 (31.6)	

*Significant

Table-3: Adverse drug effects experienced by patients [n=938]

Adverse drug reactions	Frequency	Percentage
Gastrointestinal disorders	114	17.8
Hepatotoxicity	37	5.8
Nephrotoxicity	30	4.7
CNS disorders	91	14.2
Respiratory disorders	50	7.8
Joint pain	211	32.8
Cardiovascular disorder	25	3.9
Skin allergic reactions	21	3.2
Ototoxicity	41	6.4
Others	22	3.4

Table-4: Treatment outcome of DR-TB patients [n (%)]

Treatment outcomes	Sukkur [n=616]	Larkana [n=322]	Total [n=938]
Successful outcomes	317 (51.5)	189 (58.7)	506 (53.9)
Treatment completed	40 (6.5)	25 (7.8)	65 (6.9)
Cured	277 (45.0)	164 (51.0)	441 (47.0)
Unsuccessful outcomes	299 (48.5)	133 (41.3)	432 (46.1)
Death	10 (1.6)	8 (2.5)	18 (1.9)
Failed	151 (24.5)	48 (14.9)	199 (21.2)
Lost to follow up	129 (21.9)	69 (21.4)	198 (21.1)
Transferred out	9 (1.5)	8 (2.5)	17 (1.8)

DISCUSSION

Pakistan ranks fifth among high burden TB countries and little is known about treatment outcome and serious adverse effects of anti-tuberculosis drug resistant TB. The overall treatment outcome of Drug Resistant TB patients as *successful,* which was found to be 53.9%, comprised of (*cure* 47% and *treatment completed* 6.9%), and *unsuccessful* 46.1% consisting of (*dead* 1.9%, *treatment failed* 21.1%, *lost to follow-up* 21.2% and *transferred out* 1.8%) observed in present study. Similar results have been reported from numerous studies carried out in Malaysia, Kenya and Pakistan, but less than WHO global plan to end TB epidemic.[6,10,14–17] The rate of unsuccessful treatment outcome found in present study is comparatively higher than the study carried out in India by Nair *et al*.[18]

The adverse drug reactions were found higher among the drug resistant TB patients. The artharlgia was the most frequent among adverse effects found in the current study. Similar results have been reported in a cohort study conducted at Lady Reading Hospital Peshawar, Pakistan[19], and in India[20]. Numerous studies reported in India with high percentage and prevalence of adverse drug effects, joints pain the most frequently

occurring among adverse effect are comparatively more than those in the present study.[21–23] The root causes of poor treatment outcome of drug resistant TB in the region of Sukkur and Larkana should be identified on propriety basis. Early identification, prompt management and standardized reporting of adverse drug reactions at all levels of healthcare system are needed to overcome adverse effects and enhance overall favourable outcome of DR-TB patients.

CONCLUSION

The successful treatment outcome of drug resistant TB patients was found unacceptably low and does not meet the requirement of WHO End TB strategy. The adverse drug effects were high. Artharlgia was most common adverse drug effect. The drugs regimen for DR-TB patients poses hazardous effect and needs to alter with new and effective drugs regimen.

ACKNOWLEDGMENT

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AAU: Design of work, data interpretation
AD: Drafting and critical review of intellectual content
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