ORIGINAL ARTICLE

Treatment outcomes of the drug resistant tuberculosis cases previously exposed to second line anti Tuberculosis drugs in Pakistan: A multi-center cross-sectional study

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Abstract

Objectives: To determine the treatment outcomes of the drug-resistant tuberculosis patients who were previously exposed to second line drugs.

Methods: The retrospective study was conducted at eight Programmatic Management of Drug Resistant Tuberculosis (PMDT) sites in Sindh and Balochistan. Data of patients who were previously exposed to second line drugs and re-enrolled in the drug-resistant tuberculosis register at PMDT sites in Sindh and Balochistan between 2008 and 2016 was included for analysis. Data of those still under treatment or transferred to another treatment site was excluded. Association was explored between treatment outcomes and other independent variables, while in order to identify the risk factors associated with poor treatment outcomes univariate and multivariate logistic regression was used.

Results: Overall, there were 3645 patients and 288(8%) were previously exposed to second line drugs. Of them, 95(33%) were excluded, and the final sample stood at 193; 99(51.3%) males and 94(48.7%) females. The median age of the sample was 29 years (inter-quartile range: 22-41 years). The mean duration of treatment was 20±11.14 months. Overall success rate of the re-treatment of previously treated patients was 105(54.4%). Observed relapse rate was 9(4.7%).

Conclusion: The success rate for re-treatment drug-resistant tuberculosis patients was found to be unacceptably low. New drugs and novel regimens should be made widely available.

Keywords: Drug resistance tuberculosis, Sophisticated, Second line drugs. (JPMA 69: 4; 2019)

Introduction

Multi-drug resistance tuberculosis (MDR-TB) is a disease that is caused by strain of mycobacterium tuberculosis (M.TB) that is resistant to both isoniazid and rifampicin; two of the most powerful anti-TB drugs. They may or may not be resistant to other first line drugs (FLDs) and second-line drugs (SLDs).[1-3]

Drug resistance TB has re-emerged as a primary public health threatening disease and number of cases is on the rise.[4] MDR-TB develops as a result of genetic mutation of M.TB due to improper treatment with FLDs and patient's non-compliance with the treatment.[1,5,6] It has always been a burden to national tuberculosis programmes (NTPs).[7,8]

Over the past several years, studies have reported that recurrence after successful treatment of MDR-TB is a common phenomenon. The recurrence rates after successful treatment of MDR-TB are reported from 3.2% to 4.4%.[3,4]

All people with MDR-TB don't end up with successful outcomes.[9] Some of the patients may fail or are lost to follow-up on the treatment.[10]

Re-treating DR-TB cases previously exposed to SLDs poses a challenge because of limited retreatment options and continuing exposure to close contacts.[11,12] Moreover, patients experience adverse effects due to long-term use of toxic drugs and the chances of poor outcomes are higher.[13]

The current study was planned to document the treatment outcomes of patients who were re-treated for DR-TB.

Patients and Methods

The retrospective cohort study was conducted at eight Programmatic Management of Drug Resistant Tuberculosis (PMDT) sites in Sindh and Balochistan and comprised data of patients enrolled in the DR-TB register at PMDT sites during December 2008 to July 2016. Employing purposive, non-random sampling technique for data collection, all bacteriologically-confirmed TB

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patients who were found to be rifampin-resistant on genotypic drug susceptibility testing (GXP), or detected to be drug-resistant on phenotypic universaldrug-susceptibility testing (DST) were enrolled on National Tuberculosis Programmes (NTP)-recommended regimen at all PMDT sites in Sindh and Balochistan that included Ghulam Muhammad Mahar Medical College Hospital-Sukkur, Jinnah postgraduate Medical Centre-Karachi, Chandka Medical College and Hospital-Larkana, Fatima Jinnah Chest Hospital-Quetta, Institute of Chest Diseases-Kotri, People's Medical College and Hospital-Nawabshah, Civil Hospital-Mirpurkhas and The Indus Hospital-Karachi. Those included had a previous history of exposure to SLDs and known treatment outcome of current DR-TB. Data was extracted from Electronic Numerical Recording System (ENRS) that is a uniform format for data storage provided by NTP across all PMDT sites.

Keeping the prevalence of MDR-TB at 5.7%,[14] the sample size was calculated using Openepi software.[15]

Information related to age, gender, previous FLD treatment and its outcome, previous SLD treatment and its outcome, presence of comorbid diseases, type of drug resistance, resistance with FLDs and SLDs and outcome of current DR-TB treatment was noted. Treatment outcomes were declared based on World Health Organisation (WHO) standard definitions for the first-line, previous second-line and second-line re-treatment outcomes. Treatment success included those who were either cured or completed the treatment regimen. Treatment failure included those who failed, were lost to follow-up or died.

Approval was obtained from the ethics review committee of the Dow University of Health Sciences, Karachi.

Data analysis was performed using SPSS 19. Descriptive statistics and Pearson chi-square test were employed to find association between treatment outcomes and other independent variables. In order to identify the risk factors associated with poor treatment outcomes, univariate logistic regression was used. All variables were included in univariate analysis but for multiple regression analysis only those variables were included that had $p<0.25$ and results were reported as crude and adjusted hazard ratios. Confidence level was taken at 95% and $p<0.05$ was considered statistically significant.

Results

Overall, there were 3645 patients and 288(8%) were previously exposed to second line drugs. Of them, 95(33%) were excluded, and the final sample stood at 193; 99(51.3%) males and 94(48.7%) females. The median age of the sample was 29 years (inter-quartile range [IQR]: 22-41 years).

Table-1: Demographic characteristics and previous history of study participants (n=193).

Characteristics		n	(%)
Median Age in years		29± 14.19	
Age (in years)			
	5-14	4	(2.1)
	15 - 24	64	(33.2)
	25 - 34	56	(29.0)
	35 - 44	28	(14.5)
	45 - 54	21	(10.9)
	55 - 64	14	(7.3)
	64+	6	(3.1)
Gender			
	Female	94	(48.7)
	Male	99	(51.3)
History of treatment with FLDs			
	Yes	180	(93.3)
	No	13	(6.7)
Outcome of FLD treatment *			
	Cured	18	(9.3)
	Complete	17	(8.8)
	Lost to follow up	6	(3.1)
	Failed	102	(52.8)
	Not evaluated	27	(14.0)
	Unknown	10	(5.2)
Outcome of Previous SLD treatment			
	Cured	6	(3.1)
	Complete	3	(1.6)
	Lost to follow up	18	(9.3)
	Failed	67	(34.7)
	Not evaluated	97	(50.3)
	Unknown	2	(1.0)

* n for this variable is 179 because rest of the patient did not have history of treatment with first line drugs (FLDs)
SLD: Second line drug.

Of the total, 180 (93.3) patients were previously treated on FLDs and in terms of outcome, 19 (9.3%) were cured, 17 (8.8) completed, 6 (3.1%) were lost to follow-up, 102(52.8) failed, treatment outcome for 27 (14.0%) was not evaluated and of 10 (5.2%) patients it was unknown. All patients were previously exposed to SLDs and in terms of treatment outcome, 6 (3.1%) were cured, 3 (1.6%) completed, 18(9.3%) were lost to follow-up, 67(34.7%) failed, treatment outcome of 97 (53.7%) was not evaluated, and of 2(1.0%) it was unknown (Table-1).

Of all the patients enrolled for re-treatment with SLDs, 9(4.7%) were previously cured or had completed SLD

Table-2: Current clinical characteristics of study participants (n=193).

Characteristics		n	(%)
Type of DR*			
	GXP Rif Res	6	(3.1)
	Mono	1	(0.5)
	PDR	1	(0.5)
	MDR	159	(82.4)
	XDR	26	(13.5)
History of Smoking			
	Smokers	12	(6.2)
	Non-Smoker	181	(93.8)
Comorbids			
	Chronic obstructed pulmonary disease	1	(0.5)
	Depression	2	(1.0)
	Diabetes	13	(6.7)
	Epilepsy	1	(0.5)
	Hepatitis-B	5	(2.6)
	Hepatitis-C	9	(4.7)
	Renal Disease	2	(1.0)
Mean duration of treatment in months		20	(SD ±11.14)
Baseline Sputum Smear Grading Results**			
	Negative	65	(33.7)
	1-9 AFB	20	(10.4)
	Positive 1+	29	(15.0)
	Positive 2+	30	(15.5)
	Positive 3+	32	(16.6
Resistance to Fluoroquinolones			
	Yes	108	(56.0)
	No	85	(44.0)
Outcome of DR TB re-treatment			
	Cured	95	(49.2)
	Complete	10	(5.2)
	Lost to follow up	16	(8.3)
	Failed	23	(11.9)
	Died	49	(25.4)
Categories of DR TB re-treatment outcome			
	Favourable outcome	105	(54.4)
	Unfavourable outcome	88	(45.6)

DR: Drug Resistance
*GXP Rif Res: Gene Xpert Rifampicin Resistant
Mono: Mono drug resistant (this study included resistant to Rifampicin only)
PDR: Poly Drug Resistant
MDR: Multiple Drug Resistant
XDR: Extensive Drug Resistant
**n for this variable is 176 because sputum smear results were not available for rest of the patients.

treatment. The resistance pattern of majority of the patients was MDR 159(82.4%) or XDR 26(13.5%). Only 12 (6.2%) patients were smokers while 33 (17%) patients had co-morbid diseases.

The number of patients resistant to fluoroquinolones was quiet high at 108(56%).

The treatment duration of patients who were cured was 25.7±6.7 months, those who completed 22.8±3.8 months, those who were lost to follow-up 9.4±8.9 months, those who failed 22.8±13.2 months and those who died 7.6±6.7 months.

Overall, 105 (54.4%) patients experienced favourable outcome and 88(45.6%) had unfavourable outcome (Table-2).

Gender (p=0.519), outcome of previous SLD treatment (p=0.109), type of DR (p=0.111), history of smoking

Table-3: Baseline characteristics by treatment outcomes.

Characteristics		Total	Favourable Outcome n(%)	Poor Outcome n(%)	p-value*
Age (in years)					
	5-24	69	44 (63.8)	25 (36.2)	0.014*
	25 - 34	56	29 (51.8)	27 (48.2)	
	35 - 44	27	19 (70.4)	8 (29.6)	
	45 - 54	22	7 (31.8)	15 (68.2)	
	55+	19	6 (31.6)	13 (68.4)	
Gender					
	Male	99	52 (52.5)	47 (47.5)	0.519*
	Female	94	(53 (56.4)	41 (43.6)	
Outcome of FLD treatment**					
	Cured/Complete	35	18 (51.4)	17 (48.6)	<0.001*
	Lost to follow up	6	4 (66.7)	2 (33.3)	
	Failed	102	69 (67.6)	33 (32.4)	
	Not evaluated/Unknown	37	9 (24.3)	28 (75.7)	
Outcome of Previous SLD treatment					
	Cured/Complete	9	5 (55.6)	4 (44.4)	0.109*
	Lost to follow up	18	8 (44.4)	10 (55.6)	
	Failed	67	30 (44.8)	37 (55.2)	
	Not evaluated/Unknown	99	62 (62.6)	37 (37.4)	
Type of DR resistance					
	GXP Rif Res	6	1 (16.7)	5 (83.3)	0.111***
	Mono	1	0 (0.0)	1 (100)	
	PDR	1	0 (0.0)	1 (100)	
	MDR	159	91 (57.2)	68 (42.8)	
	XDR	26	13 (50.0)	13 (50.0)	
History of Smoking					
	Smokers	12	6 (50.0)	6 (50.0)	0.752*
	Non-Smoker	181	99 (54.7)	82 (45.3)	
Co-morbids					
	Yes	160	87 (54.4)	73 (45.6)	0.986*
	No	33	18 (54.4)	15 (45.5)	
Baseline Sputum Smear Grading Results****					
	Negative	65	45 (69.2)	20 (30.8)	0.028*
	1-9 AFB	20	10 (50.0)	10 (50.0)	
	Positive 1+	29	13 (44.8)	16 (55.2)	
	Positive 2+	30	15 (50.0)	15 (50)	
	Positive 3+	32	12 (37.5)	20 (62.5)	
Resistance to Fluoroquinolones					
	Yes	108	55 (50.9)	53 (49.1)	0.274*
	No	85	50 (58.8)	35 (41.2)	

*The p value has been calculated using Chi square test.**n for this variable is 179 because rest of the patient did not have history of treatment with FLDs. ***Fisher Exact Test p-value ****n for this variable is 176 because sputum smear results were not available for rest of the patients
FLD: First line drugs
SLD: Second line drugs.

(p=0.752), presence of comorbids (p>0.999), resistance to fluoroquinolones (p=0.274) were not significantly associated with poor treatment outcomes. However, older age (p=0.014), outcome of FLD treatment (p<0.001), and higher bacterial load on sputum smear grading at baseline (p=0.028) were significantly positively associated with poor treatment outcome. (Table-3)

Univariate analysis indicated that older age (p=0.005), outcome of previous FLD treatment being 'not evaluated' or 'unknown' (p=0.019), higher sputum smear grading at baseline (p<0.05) were factors significantly associated with poor treatment outcomes.

Multiple logistic regression indicated that patients with older age were more likely to have poor treatment outcomes (p=0.008). Moreover, patients who had

Table-4: Factors associated with poor treatment outcome.

Characteristics		Univariate analysis		Multivariate analysis	
		OR[a] (95% CI)	p-value	OR[b] (95% CI)	p-value
Age (in years)	1.03 (1.00-1.05)	0.005		1.03 (1.00-1.06)	0.008
Gender					
	Male	1			
	Female	0.85 (0.48-1.50)	0.591	1.61 (0.75-3.42)	0.215
Outcome of FLD treatment					
	Cured/Complete	1		1	
	Lost to follow up	0.52 (0.08-3.27)	0.493	0.84 (0.11-6.12)	0.863
	Failed	0.50 (0.23-1.10)	0.088	0.64 (0.27-1.53)	0.322
	Not evaluated/Unknown	3.29 (1.20-8.97)	0.019	4.52 (1.39-14.63)	0.011
Outcome of Previous SLD treatment					
	Cured/Complete	1			
	Lost to follow up	1.56 (0.31-7.81)	0.586		
	Failed	1.54 (0.38-6.25)	0.544		
	Not evaluated/Unknown	0.74 (0.18-2.95)	0.676		
History of Smoking					
	Smokers	1			
	Non-Smoker	0.82 (0.25-2.66)	0.752		
Co-morbids					
	Yes	1			
	No	0.99 (0.46-2.10)	0.986		
Baseline Sputum Smear Grading Results					
	Negative	1			
	1-9 AFB	2.25 (0.80-6.25)	0.12	1.13 (0.30-4.13)	0.853
	Positive 1+	2.76 (1.12-6.82)	0.026	2.35 (0.83-6.60)	0.105
	Positive 2+	2.25 (0.92-5.47)	0.073	1.83 (0.68-4.89)	0.227
	Positive 3+	3.75 (1.54-9.11)	0.003	3.48 (1.24-9.71)	0.017
Resistance to Fluoroquinolones					
	Yes	1			
	No	0.72 (0.40-1.28)	0.275		

OR[a]: Unadjusted odd ratios
OR[b]: Odds ratio adjusted for age, outcome of FLD treatment, sputum smear grading
CI: Confidence Interval.
FLD" First line drugs
SLD: Second line drugs.

previous FLD outcome 'not evaluated' or 'unknown' were more likely to have poor treatment outcome (p=0.011). Positive 3+ sputum smear grading at the baseline was significantly associated with poor treatment outcome (p=0.017) (Table-4).

Discussion

The study showed that 45.6% of the patients re-treated for DR-TB had poor treatment outcome. While older age, higher sputum smear grading at baseline and previous FLD treatment outcome were the factors associated with poor treatment outcomes. Patients whose previous FLD outcome was not evaluated (who were treated at some private facility and did not fit any WHO outcome criteria) or whose treatment outcome for FLDs was unknown or undocumented (basically patients at private facilities) were at the higher risk of poor treatment outcome.

The relapse rate in DR-TB is found to be 4.7%. Though the primary outcome of the study was not to evaluate the relapse rate, we found the proportion of the patient coming for re-treatment after previous successful treatment (either treatment completed or cured) with DR-TB. The relapse rate was coherent to that reported in other studies.[2,3,16]

Overall, the current study shows treatment success rate of 54.4% that is quite lower than previously reported in Pakistan, Kenya and Malaysia.[10,17-20] However, treatment success rate is similar to that reported by some studies.[6]

The treatment failure rate and mortality rates observed in our study are quite higher than those reported in other studies. The lost-to-follow-up rate is, however, comparable to literature.[10,17-19,21] The reason might be that our cohort included patients previously exposed to SLDs and hence left with more number but least effective drugs for treatment.

Univariate analysis identified older age, higher sputum smear grading and previous FLD outcomes as factors associated with poor treatment outcome.

However, after controlling for different variables in multivariate analysis, the results didn't differ and the same factors were found to be associated with poor treatment outcomes. The findings of this study are coherent with earlier findings.[6,8,10,17,21,22]

DR-TB develops as a result of poor treatment with FLDs. This single point provides enough support to our results as we found that patients who had previous FLD outcome either 'not-evaluated' or 'unknown' were at the higher risk of poor treatment outcome. Usually in our setting patients who are treated with FLDs for susceptible TB at public hospitals have treatment cards with details of treatment provided along with treatment outcomes. However, most private clinics don't provide treatment cards and treatment details to the patients or don't treat the patients and declare the treatment outcomes as per NTP guidelines. Therefore, their FLD treatment outcome is labelled as not evaluated or unknown.

It is evident that there is a great scope of improvement in the susceptible TB Programme. Regular surveillance of the programme highlighting both its success and failure is important to find weak areas which need intervention for better programme outcome. Public-private partnership should be strengthened and treatment of susceptible TB by unregistered and untrained private practitioners should be strictly banned. Availability of anti-TB drugs should be discouraged at private pharmacies. Better collaboration and coordination between the NTP and the private sector through the public-private approach should be established and there should be strict and improved reporting system for all facilities where patients are diagnosed and treated for TB. There is a need to implement and improve public-private projects, and private practitioners need to be appropriately trained to report TB patients according to NTP guidelines.

Conclusion

The success rate for re-treatment DR TB patients was found to be unacceptably low, indicating that the custom regimen being used to treat re-treatment of DR-TB patients is insufficient. Therefore new DR-TB drugs and novel regimens are required, and should be made widely available across the country.

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Disclosure: The analysis was performed on secondary data collected for one of the author's Master's thesis for which MDR-TB patients were followed up for six months after the treatment initiation and later on the final treatment outcomes of the study participants were recorded.

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References

1. Ormerod LP. Multidrug-resistant tuberculosis (MDR-TB): epidemiology, prevention and treatment. Br Med Bull 2005; 73: 17-24.
2. Becerra MC, Appleton SC, Franke MF, Chalco K, Bayona J, Murray MB, et al. Recurrence after treatment for pulmonary multidrug-resistant tuberculosis. Clin Infect Dis 2010; 51: 709-11.
3. Lee J, Lim H, Cho Y, Park Y, Lee S, Yang S, et al. Recurrence after successful treatment among patients with multidrug-resistant tuberculosis. Int J Tuberc Lung Dis 2011; 15: 1331-3.
4. Ennassiri W, Jaouhari S, Cherki W, Charof R, Filali-Maltouf A, Lahlou O. Extensively drug-resistant tuberculosis (XDR-TB) in Morocco. J Glob Antimicrob Resist 2017; 11: 75-80.
5. Mukherjee JS, Rich ML, Socci AR, Joseph JK, Virú FA, Shin SS, et al. Programmes and principles in treatment of multidrug-resistant tuberculosis. Lancet 2004; 363: 474-81.
6. Johnston JC, Shahidi NC, Sadatsafavi M, Fitzgerald JM. Treatment outcomes of multidrug-resistant tuberculosis: a systematic review and meta-analysis. PloS one 2009; 4: e6914.
7. Lange C, Abubakar I, Alffenaar JW, Bothamley G, Caminero JA, Carvalho ACC, et al. Management of patients with multidrug-resistant/extensively drug-resistant tuberculosis in Europe: a TBNET consensus statement. Eur Respir J 2014; 44: 23-63.
8. Morris MD, Quezada L, Bhat P, Moser K, Smith J, Perez H, et al. Social, economic, and psychological impacts of MDR-TB treatment in Tijuana, Mexico: a patient's perspective. Int J Tuberc Lung Dis 2013; 17: 954-60.
9. Brode SK, Varadi R, McNamee J, Malek N, Stewart S, Jamieson FB, et al. Multidrug-resistant tuberculosis: treatment and outcomes of 93 patients. Can Respir J 2015; 22: 97-102.
10. Khan MA, Mehreen S, Basit A, Khan RA, Jan F, Ullah I, et al. Characteristics and treatment outcomes of patients with multi-drug resistant tuberculosis at a tertiary care hospital in Peshawar, Pakistan. Saudi Med J 2015; 36: 1463-71.
11. Yang TW, Park HO, Jang HN, Yang JH, Kim SH, Moon SH, et al. Side effects associated with the treatment of multidrug-resistant tuberculosis at a tuberculosis referral hospital in South Korea: A retrospective study. Medicine (Baltimore) 2017; 96: e7482.
12. Törün T, Güngör G, Özmen I, Bölükbaşı Y, Maden E, Bıçakçı B, et al.

Side effects associated with the treatment of multidrug-resistant tuberculosis. Int J Tuberc Lung Dis 2005; 9: 1373-7.
13. Chung-Delgado K, Guillen-Bravo S, Revilla-Montag A, Bernabe-Ortiz A. Mortality among MDR-TB cases: comparison with drug-susceptible tuberculosis and associated factors. PloS one 2015; 10: e0119332.
14. Wang SF, Zhou Y, Pang Y, Zheng HW, Zhao YL. Prevalence and Risk Factors of Primary Drug-Resistant Tuberculosis in China. Biomed Environ Sci 2016; 29: 91-8.
15. Dean A, Soe M. OpenEpi: Open Source Epidemiologic Statistics for Public Health, Version 23, 2011.
16. Chen MY, Lo YC, Chen WC, Wang KF, Chan PC. Recurrence after Successful Treatment of Multidrug-Resistant Tuberculosis in Taiwan. PloS one 2017; 12: e0170980.
17. Qadeer E, Fatima R, Fielding K, Qazi F, Moore D, Khan MS. Good quality locally procured drugs can be as effective as internationally quality assured drugs in treating multi-drug resistant tuberculosis. PloS one 2015; 10: e0126099.
18. Elmi OS, Hasan H, Abdullah S, Mat Jeab MZ, Ba Z, Naing NN. Treatment Outcomes of Patients with Multidrug-Resistant Tuberculosis (MDR-TB) Compared with Non-MDR-TB Infections in Peninsular Malaysia. Malays J Med Sci 2016; 23: 17-25.
19. Yew WW, Chan CK, Chau CH, Tam CM, Leung CC, Wong PC, et al. Outcomes of patients with multidrug-resistant pulmonary tuberculosis treated with ofloxacin/levofloxacin-containing regimens. Chest 2000; 117: 744-51.
20. Mibei D, Kiarie J, Wairia A, Kamene M, Okumu M. Treatment outcomes of drug-resistant tuberculosis patients in Kenya. Int J Tuberc Lung Dis 2016; 20: 1477-82.
21. Nair D, Velayutham B, Kannan T, Tripathy J, Harries A, Natrajan M, et al. Predictors of unfavourable treatment outcome in patients with multidrug-resistant tuberculosis in India. Public Health Action 2017; 7: 32-8.
22. Janmeja A, Aggarwal D, Dhillon R. Analysis of treatment outcome in multi-drug resistant tuberculosis patients treated under programmatic conditions. Int J Res Med Sci 2017; 5: 2401-5 .