Original Article

Assessment of treatment outcomes of daily fixed-dose combination therapy among drug-sensitive pulmonary tuberculosis patients: A prospective study from Bengaluru, India

Sumana M[1], Saraswathi S[1], Amita Mukhopadhyay[2], Ipsita Debata[3], TS Ranganath[1]

[1]Department of Community Medicine, Bangalore Medical College and Research Institute, Bengaluru, Karnataka, India, [2]Department of Hospital and Health Management, Institute of Health Management Research Bangalore, Bengaluru, Karnataka, India, [3]Department of Community Medicine, Kalinga Institute of Medical Sciences, Bhubaneswar, Odisha, India

Abstract

Context: The annual incidence cases report depicts India as having the highest tuberculosis (TB) burden globally. Following a programmatic change, the daily fixed-dose combination (FDC) anti-TB treatment regimens were introduced by the Indian government's National Tuberculosis Elimination Program (NTEP). **Aims:** The aim of the study was to assess the treatment outcomes among drug-sensitive pulmonary TB patients receiving daily FDC drugs and the associated factors influencing the treatment outcomes. **Settings and Design:** A prospective study was conducted among 300 drug-sensitive pulmonary TB cases in the Bruhat Bengaluru Mahanagara Palike (BBMP) area. **Materials and Methods:** The TB units and designated microscopic centers (DMCs) were selected by multistage random sampling. Data were collected through a pre-tested and semi-structured questionnaire. Patients were followed up until treatment completion. **Statistical Analysis Used:** Data were compiled and analyzed using IBM Statistical Package for Social Sciences (SPSS) statistics version 20.0. Descriptive statistics and the Chi-square test were used for interpretation. A *P*-value less than 0.05 was considered statistically significant. **Results:** Around 86.33% of patients were cured, 4% had completed treatment, and 1% had treatment failure. Older age, human immunodeficiency virus (HIV) reactive status, alcohol intake, tobacco use, and migrants were associated with poor outcomes. **Conclusions:** The daily FDC regimen had better outcomes than intermittent regimens. Smokers, alcoholics, migrants, and patients with co-morbidity need to be given priority in management as they are prone to poorer outcomes.

Keywords: Fixed-dose combination, NTEP, pulmonary tuberculosis, treatment compliance, treatment outcome

Introduction

India is the highest tuberculosis (TB) burden country in the world, contributing to nearly one-fourth (27%) of the global total in 2019. This marks another milestone year for the TB surveillance effort in India, with a record-high notification of 24 lakh cases, an increase of over 12% compared to 2018.[1]

Address for correspondence: Dr. Ipsita Debata, Department of Community Medicine, Kalinga Institute of Medical Sciences, Kushabhadra Campus, 5, KIIT Rd, Bhubaneswar - 751 024, Odisha, India.
E-mail: drdebataipsita@gmail.com

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The Revised National Tuberculosis Control Programme (RNTCP) has treated TB in India since 1997. By March 2006, the entire country was covered under "Directly Observed Treatment Short-course" (DOTS) with an alternate day regimen.[2] The nation drafted and approved a National Strategic Plan (NSP) for TB elimination 2017–2025, adopting the END TB strategy to achieve Sustainable Development Goal (SDG) 3.3.[3] Since October 2017, the Joint Monitoring Mission has advised switching from an intermittent to a daily fixed-dose combination (FDC) regimen due to the high rate of relapse and the development of drug resistance with intermittent regimens.[4] The principle for treating drug-sensitive pulmonary TB with a daily regimen is to administer FDCs of first-line anti-TB drugs in appropriate weight bands.[2] The state of Karnataka also implemented the daily FDC, 99 DOTS, and reporting of adverse drug events (ADEs) under these guidelines in October 2017. Since the implementation of this new daily regimen, not many studies have been conducted in this part of India to evaluate the programmatic outcomes among microbiologically confirmed and drug-sensitive pulmonary TB patients. A few studies conducted outside of India have not revealed a statistically significant difference between the program's daily and three-weekly medication policies and treatment outcomes.[5,6] Hence, this study was conducted to assess the treatment outcomes among drug-sensitive pulmonary TB patients receiving daily FDC drugs and the associated sociodemographic and clinical factors influencing the treatment outcomes. The findings can be analyzed to advocate for necessary changes to the new daily regimen.

Materials and Methods

A hospital-based prospective study was carried out in selected TB units (TUs) and designated microscopic centers (DMCs) in the Bruhat Bengaluru Mahanagara Palike (BBMP) area from November 2019 to June 2020. Ethical clearance was obtained from the Institutional Ethical Committee of Bangalore Medical College and Research Institute (Ref no. BMC/PG/124/2018-19) before commencing the study. Permission was also sought from the district tuberculosis officer (DTO). The multistage random sampling method was followed while selecting the TUs and DMCs. Out of 22 TUs in the BBMP area, 15 TUs were selected by simple random sampling in the first stage. Then, from each of these selected TUs, two DMCs were further selected randomly in the next stage. A total of 30 DMCs were included. The sample size was calculated based on the "RNTCP Annual Status Report: India TB Report 2018," in which 27,397 registered TB cases were in Karnataka and the cure rate was 77%.[7] With an absolute precision of 5% and an attrition rate of 5%, the sample size calculated was 300. Microbiologically confirmed and drug-sensitive TB patients, aged 18 years and older, enrolled in these selected DMCs were included in the study. Extrapulmonary TB cases were excluded. The patients fulfilling the inclusion criteria and consenting to the study were included in the study until the sample size was reached. A semi-structured and pre-tested questionnaire was used to collect information regarding socio-demographic profiles, co-morbidities, and other relevant information affecting treatment outcomes. Data were collected from study participants by the personal interview method at the time of enrollment. Diagnosis details – concerning sputum testing, chest X-ray, and cartridge based nucleic acid amplification test (CBNAAT) results – were collected from the DMC records. Socio-environmental factors were assessed by visiting the subjects' houses. Follow-up was done to see sputum conversion status at the end of the intensive phase (IP) and continued until the end of treatment. The treatment outcome was then determined based on sputum conversion and clinical improvement at the end of the continuation phase.

Data were compiled and analyzed using IBM Statistical Package for Social Sciences (SPSS) statistics version 20.0 (developed by IBM in Chicago, USA). Descriptive statistics and the Chi-square test were used for interpretation. A *P*-value less than 0.05 was considered statistically significant.

Results

A total of 300 pulmonary TB patients were included in the study. There were 185 (61.66%) males and 115 (38.34%) females. The mean age of the study participants was 38.30 ± 15.62 years. Most participants were Hindu, that is, 221 (73.67%). Around 215 (71.67%) participants were married, and 146 (48.67%) were educated until high school. The sociodemographic characteristics are depicted in Table 1.

In the present study, among 300 pulmonary TB cases, 253 (84.33%) were newly diagnosed cases. 47 (15.67%) were

Table 1: Sociodemographic characteristics of the study participants

Sociodemographic variable	Frequency (%) (*n*=300)
Gender	
Male	185 (61.66)
Female	115 (38.34)
Religion	
Hindu	221 (73.67)
Muslim	68 (22.66)
Christian	11 (03.67)
Marital status	
Married	215 (71.67)
Unmarried	82 (27.33)
Widow/widower	03 (1)
Educational Status	
High school	146 (48.67)
Middle school	38 (12.67)
Illiterate	75 (25)
Occupational status	
Skilled labor	35 (11.67)
Semi-skilled labor	40 (13.33)
Unskilled labor	78 (26)
Unemployed	94 (31.34)
Socioeconomic status*	
Upper lower class	109 (36.33)
Lower class	143 (47.67)

*Modified Kuppuswamy socioeconomic status classification[8]

previously treated cases. Among these, 26 (8.68%) were recurrent cases, and nine (3%) were patients for whom the previous treatment outcome was unknown. The treatment outcomes among the study participants after the continuation phase are shown in Figure 1.

The case fatality rate among TB cases in the present study was 6.67%. Among the 20 subjects who died during treatment, 16 died during the IP, and four died during the continuation phase. As shown in Table 2, the case fatality rate was higher among females (7.83%) as compared to males (5.95%) and among human immunodeficiency virus (HIV)-reactive cases (60%) as compared to HIV non-reactive (4.83%). The case fatality rate among diabetics and non-diabetics in this study was found to be equal at 6.67%.

Out of 300 microbiologically confirmed drug-sensitive pulmonary TB cases, 11 (3.67%) remained positive at the end of the IP, and among those six were diabetic. At the end of the continuation phase, 3 (1%) were positive for TB bacilli on Ziehl-Neelsen staining, thus resulting in treatment failure. The sputum conversion status is depicted in Table 3.

The treatment outcome was further categorized into "treatment success," defined as participants who completed their treatment and were declared cured at the end of the treatment course, and "treatment unsuccessful," defined as participants who were lost to follow-up, had treatment failure, or died at the end of the treatment course. Age more than 50 years ($P = 0.008$), type of residence ($P = 0.010$), and presence of overcrowding ($P = 0.021$) were found to be significantly associated with adverse treatment outcomes, as shown in Table 4.

The rate of unsuccessful treatment was significantly higher among HIV-infected TB patients (70.0%) as compared to HIV non-reactive patients (10.3%). History of alcohol intake, tobacco smoking, and chewing were found to be significantly associated with unsuccessful treatment outcomes, as seen in Table 5.

Table 2: Comparison of different variables between the treatment outcome groups

Study variable	Treatment outcome	
	Alive (*n*=280) *n* (%)	Dead (*n*=20) *n* (%)
Gender		
Male	174 (94.05)	11 (05.95)
Female	106 (92.17)	9 (07.83)
Age		
≤50 years	232 (95.47)	11 (04.53)
>50 years	48 (84.21)	9 (15.79)
HIV status		
Non-reactive	276 (95.17)	14 (04.83)
Reactive	4 (40.00)	6 (60.00)
Diabetic status		
Diabetic	56 (93.33)	4 (06.67)
Non-diabetic	224 (93.33)	16 (06.67)
Tobacco smoking		
Smoker	56 (90.32)	6 (09.68)
Non-smoker	224 (94.12)	14 (05.88)

Discussion

A total of 300 drug-sensitive pulmonary TB patients on daily FDC regimens were included in our study. There were 185 (61.66%) males and 115 (38.34%) females. The mean age of the study participants was 38.30 ± 15.62 years. Most participants were Hindu, that is, 221 (73.67%), 215 (71.67%) participants were married, and 146 (48.67%) were educated until high school. A study by Divakar M *et al.*[9] in Tumkur, Karnataka, had 70 (57.9%) males and 51 (42.1%) females; the median age of study participants was 37 (49.5–26.5) years, and most of the participants were Hindu and married. All these findings were quite similar to our study. In our study, the treatment outcomes reported were 259 (86.33%) were cured, 20 (6.67%) died, 14 (4.67%) were lost to follow-up, and three (1%) had treatment failure. The overall treatment success rate was 87.67%. In the treatment outcomes reported by Prajapati *et al.*[10] in Ahmedabad, 69.1% completed treatment, 20.9% were cured, and 3.6% died among the newly detected pulmonary TB patients. The overall treatment success rate was 87.9% in the new treatment category. A study by Teferi M Y *et al.*[11] in Ethiopia also reported a similar treatment success rate of 82.5% among TB patients. It has been

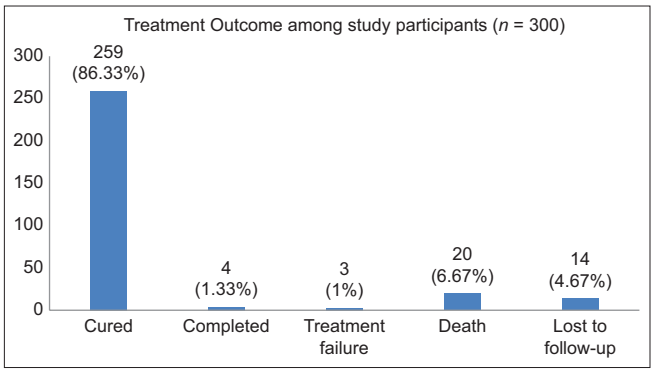

Figure 1: Treatment outcome among the study participants

Table 3: Sputum conversion among the study participants (*n*=300)

Period of testing	Ziehl-Neelsen (ZN) stain				CBNAAT	Total positives	Total negative
	Grade of sputum smear microscopy						
	Scanty	1+	2+	3+	MTb Detected†		
At the time of diagnosis	25	138	20	24	93	300	-
End of IP	0	7	0	0	4	11	273
End of CP	1	2	0	0	0	3	263

†MTB=*Mycobacterium tuberculosis*

Table 4: Association between socio-demographic and socio-environmental factors and treatment outcome

Study variable	Treatment outcome [*n* (%)]			χ^2, (*P*)*
	Treatment success (*n*=263)	Treatment unsuccessful (*n*=37)	Total (*n*=300)	
Gender				
Male	161 (87.0%)	24 (13.0%)	185 (100%)	0.183, (0.721)
Female	102 (88.7%)	13 (11.3%)	115 (100%)	
Age				
≤50 years	219 (90.1%)	24 (9.9%)	243 (100%)	7.140, (0.008)
>50 years	44 (77.2%)	13 (22.8%)	57 (100%)	
Literacy				
Illiterate	69 (92.0%)	6 (08.0%)	75 (100%)	1.737, (0.227)
Literate	194 (86.2%)	31 (13.8%)	225 (100%)	
Marital status				
Married	187 (87.0%)	28 (13.0%)	215 (100%)	0.334, (0.698)
Unmarried/widow	76 (89.4%)	9 (10.6%)	85 (100%)	
Residence at BBMP				
Permanent resident	248 (89.2%)	30 (10.8%)	278 (100%)	8.336, (0.010)
Migrant	15 (68.2%)	7 (31.8%)	22 (100%)	
Overcrowding				
Present	24 (75.0%)	8 (25.0%)	32 (100%)	5.316, (0.021)
Absent	239 (89.2%)	29 (10.8%)	268 (100%)	
Ventilation				
Adequate	179 (89.1%)	22 (10.9%)	201 (100%)	1.085, (0.297)
Inadequate	84 (84.8%)	15 (15.2%)	99 (100%)	
Indoor air pollution				
Present	50 (87.7%)	7 (12.3%)	57 (100%)	0.0002, (0.989)
Absent	213 (87.7%)	30 (12.3%)	243 (100%)	

*P<0.05 considered statistically significant

Table 5: Association between clinical factors and habits with treatment outcome

Study variable	Treatment outcome [*n* (%)]			χ^2, (*P*)†
	Treatment success (*n*=263)	Treatment unsuccessful (*n*=37)	Total (*n*=300)	
Type of case based on history of TB treatment				
New	222 (87.7%)	31 (12.3%)	253 (100%)	0.10, (1.00)
Previously treated	41 (87.2%)	6 (12.8%)	47 (100%)	
HIV status				
Reactive	3 (30.0%)	7 (70.0%)	10 (100%)	31.817, (<0.00001)
Non-reactive	260 (89.7%)	30 (10.3%)	290 (100%)	
Diabetic mellitus				
Diabetic	53 (88.3%)	7 (11.7%)	60 (100%)	0.031, (1.00)
Non-diabetic	210 (87.5%)	30 (12.5%)	240 (100%)	
Alcohol consumption				
Yes	51 (76.1%)	16 (23.9%)	67 (100%)	10.639, (0.001)
No	212 (91.0%)	21 (09.0%)	233 (100%)	
Tobacco smoking status				
Smoker	47 (75.8%)	15 (24.2%)	62 (100%)	11.003, (0.0009)
Non-smoker	217 (91.1%)	21 (8.9%)	238 (100%)	
Tobacco chewing status				
Yes	21 (63.6%)	12 (36.4%)	33 (100%)	19.803, (<0.00001)
No	242 (90.6%)	25 (9.4%)	267 (100%)	

†P<0.05 is considered statistically significant

estimated that nearly 20% of all TB cases in India also suffer from DM.[1] Similarly, in our study, 20% of subjects were diabetic. Diabetes triples the risk of TB and can worsen the clinical course of TB. TB can also worsen blood sugar control in people with diabetes. In our study, 10% of diabetics remained positive at the end of the IP, and 1.66% remained positive at the end of CP, resulting in treatment failure. Similar results were found in a study by Viswanathan V *et al*.[12] in which 14.7% of the diabetic group remained sputum-positive at the end of IP. In 2018, 36,510 TB-HIV cases were notified in the country, out of which

treatment success was achieved in 73%, failure in 1%, 11% died, 5% were lost to follow-up, 8% were transferred out, and 1% had treatment regimen change.[7] In contrast, the present study shows a loss-to-follow-up rate among TB-HIV cases of 10% and a case fatality rate of 60%. However, among TB-HIV negative cases, the case fatality rate was only 4.82%, indicating higher mortality among TB-HIV-co-infected cases. A study by O Babatunde *et al*.[13] found that the treatment success rate was lower in TB-HIV-co-infected patients (64.1%) than in TB-HIV–negative patients (73.6%). Similarly in the present study, the treatment success rate among TB-HIV cases, it was only 30%, and among HIV-negative cases was 89.7%, indicating that HIV co-infection affects TB treatment outcomes adversely. Studies have also shown that the default rate was high among patients who could not access medicines when they migrated to a new place.[14,15] Similarly, in this study, non-compliance and unsuccessful treatment outcomes were found to be more common among temporary residents of BBMP who had migrated to their hometown due to unemployment during the coronavirus disease 2019 (COVID-19) pandemic. A study by VD Karanjekar *et al*.[16] revealed treatment success rates of 78.3%, 65%, and 75.6% among categories I, II, and III, respectively. However, in our study, the treatment success rate among newly diagnosed cases was almost equal to that of previously treated cases. This may be due to the recent change in guidelines, in which previously treated cases were switched to the shorter regimen of 6 months. In this study, 20.67% of the study subjects were smokers. Smokers and patients who consumed alcohol had significantly high rates of loss to follow-up, death rate, and unsuccessful treatment outcomes as compared to non-smokers. In a study by V. Mahishale *et al*.,[17] 32.21% of the study participants were ex-smokers and current smokers. The treatment success rate among non-smokers was 92.4%, among ex-smokers was 77.7%, and among current smokers was 72.5%. Drinking alcohol has been linked to treatment failure and a tendency toward side drug effects. This could be because people who drink alcohol missed more doses during TB treatment or alcohol may alter the immune system's reaction to *M. tuberculosis*, which could result in treatment failure or a delayed response to treatment.[18–20] These findings highlight the urgent need for smoking and alcohol cessation programs at all levels of health care services, not only to decrease the prevalence of these habits among TB patients but also to reduce the overall incidence of TB.

Limitation

Although our study was the first of its kind to evaluate the newly implemented FDC regimen in Karnataka and would contribute significantly to policymakers and researchers, all factors could not be evaluated to determine their association with TB treatment outcomes. Factors related to healthcare service delivery and healthcare providers that can have a significant impact on treatment outcomes could not be assessed in our study.

Conclusion

In our study, the overall treatment success rate was 87.67% (86.33% were cured, 6.67% died, 4.67% were lost to follow-up, and 1% had treatment failure). Advancing age, migratory resident status, overcrowding, female gender, alcohol and tobacco intake, and HIV-reactive status had significant adverse treatment outcomes. Further studies on the identification of challenges or drawbacks in the program and assessment of the long-term outcomes of the new regimen, such as relapse, recurrence, and conversion to drug resistance are warranted.

Recommendation

Nikshay portal should be utilized for online referral, transfer, and linking of migrant cases to a health facility at their place; priority must be given to TB patients with co-morbidity with intensified monitoring and supervision, a referral system for linking patients with substance use problems to de-addiction centers, and interventions like pharmacological treatment for cessation of smoking in TB patients can be implemented in routine clinical practice. Training sessions can be planned for the same involving primary care physicians who are the first level of contact for TB patients and who are also responsible for providing follow-up care.

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Conflicts of interest

There are no conflicts of interest.

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