(International Print/Online Journal)

SJIF IMPACT FACTOR: 5.565
PUBMED-National Library of Medicine ID-101739732

ISSN (Print): 2209-2870
ISSN (Online): 2209-2862

International Journal of Medical Science and Current Research (IJMSCR)
Available online at: www.ijmscr.com
Volume3, Issue 3, Page No: 556-565
May-June 2020

Efficacy and Safety of Category-1 Anti-Tubercular Drugs in Fixed Dose Combination – A Prospective Observational Study in a Tertiary Care Hospital

Sathya priyadharisini R[1], Vanitha Samuel[2*], Pandian K[3], Nirmala P[4]
[1]Post Graduate, [2, 3] Professor and Head, [4]Professor
[1, 2, 4] Department of Pharmacology, [3]Department of Chest and TB
Rajah Muthiah Medical College, Chidambaram 608002

***Corresponding Author:**
Vanitha Samuel
Professor and Head, Department of Pharmacology,
Rajah Muthiah Medical College, Chidambaram 608 002, TN, India

Type of Publication: Original Research Paper
Conflicts of Interest: Nil

ABSTRACT

Background: Treatment of Category-1 Tuberculosis(TB) as a Fixed Dose Combination(FDC) was implemented by RNTCP(Revised National Tuberculosis Control Program) since 0ct 2017. Since challenges remain to demonstrate its efficacy, the objective of this study was to assess the efficacy and safety of Category-1 anti-tuberculous drugs given as FDC by Directly Observed Treatment Short course(DOTS).

Materials and Methods: This prospective, observational study was conducted for a period of 12 months in the TB and Chest department at Rajah Muthiah Medical College and Hospital. A total of 100 Category-1 patients, of both sexes, with pulmonary and extra-pulmonary TB were evaluated and their RNTCP treatment cards were analysed for efficacy and safety.

Results: For Pulmonary Tuberculosis(PTB) patients, change in sputum conversion was 97.2% at the end of 2 months and 98.5% at the end of 6 months while 1.4% remained sputum positive at the end of 6 months. X-rays monitored at the end of six months showed 81.9% cure rate, 1.3% treatment failure and 16.6% patients who were left with cavity, post treatment. Extra-pulmonary Tuberculosis(EPTB) patients showed 100% cure rate confirmed by investigations at the end of six months.

Conclusion: We conclude that Category-1 anti-tuberculous treatment given as FDC showed greater efficacy and safety when administered by DOTS as evidenced by X-rays for PTB and diagnostic Cartridge-based nucleic acid amplification test(CBNAAT) for PTB and EPTB.

Keywords: Cartridge-based nucleic acid amplification test (CBNAAT), Directly Observed Treatment Short course (DOTS), Extra-pulmonary Tuberculosis (EPTB), Fixed dose combination(FDC), Pulmonary Tuberculosis (PTB), Tuberculosis (TB).

INTRODUCTION

Tuberculosis(TB) remains a major concern of ill health and one of the leading causes of death from a single infectious agent, *Mycobacterium tuberculosis.* India has the world's highest incidence of TB, with 2.8 million cases reported annually, and accounts for more than a quarter of the global TB burden.[1]

Effective treatment of TB patients under Directly Observed Treatment Short course (DOTS) with

multidrug chemotherapy instituted by Revised National Tuberculosis Control Program (RNTCP) consisting of the first line drugs - Isoniazid(H), Rifampicin(R), Pyrazinamide(Z) and Ethambutol(E) for Category-1 (pulmonary tuberculosis(PTB) and extra-pulmonary tuberculosis(EPTB) - newly diagnosed), still remains the cornerstone of modern approach.

Previously, a standardized intermittent, thrice weekly regimen was followed that included HRZE (600/450/1500/1200 mg) in the intensive phase for two months and HR(600/450mg) in continuation phase for four months.[2] Although this is an effective strategy, emergence of drug resistance due to poor compliance[3] and also increased adverse effects has opened up new horizons in therapy of TB.

Currently, a daily fixed dose combination (FDC) regimen schedule is followed with HRZE (75/150/400/275 mg per tablet) given in the intensive phase for two months and HRE (75/150/275mg per tablet) given in the continuation phase for four months. The number of pills for each patient varies with the bodyweight.[4] This modality of treatment was started in India from Oct 2017[5] onwards for Category-1 TB patients. Efficacy of the present regimen as evidenced by x-rays for PTB and diagnostic Cartridge-based nucleic acid amplification test(CBNAAT) analysis for PTB/EPTB remains in vogue in the recent years.[6-9]

World health organization (WHO, 2004) defines pharmacovigilance as "the science and activities relating to the detection, assessment, understanding and prevention of adverse drug reactions, or any other medicine-related problems".[10] Few studies [11,12] have been conducted to assess the safety of anti-tuberculosis drugs using the WHO-UMC system for standardised case causality assessment.

The objectives of the study was to assess the efficacy and safety of anti-tubercular drugs Category-1 (newly diagnosed PTB and EPTB) in fixed dose combination currently followed by RNTCP guidelines.

MATERIALS & METHODS

Study Design: The present study was a prospective, observational study done in 100 TB patients for a period of one year.

Study Setting: Study approval with proposal number IHEC/0481/2018, was obtained from Institutional Human Ethics Committee before initiating the study. Informed consent was procured from all the subjects prior to their enrolment in the study. The study was carried out in TB & Chest department of Rajah Muthiah Medical College Hospital, Chidambaram, a tertiary care hospital.

Study Period: Study was carried out from December 2018 to December 2019

Study Participants:

Inclusion Criteria: Patients of both sexes, in the age group of 13-60 years, who were newly diagnosed as PTB/EPTB were included in the study. Category-1 anti- tuberculosis drug treatment was prescribed by the physician attending Chest and TB department. Males with history of alcoholism/ smoking were also included in the study.

***Exclusion Criteria*:** Patients with relapse, default, dropout, patients with multi drug resistant TB, HIV and other co-morbidities like diabetes, hypertension were excluded from the study. Patients who were not willing to include themselves and patients less than 12 years or above 60 years of age were excluded.

RNTCP Regimen for Category-1 TB: The recommended daily dose regimen for Category-1 TB as per RNTCP guidelines, 2016[4] is as follows;

Volume 3, Issue 3; May-June 2020; Page No.556-565

Table 1- Daily FDC Regimen schedule for adult TB patients under RNTCP

Type of case	Weight category	Number of tablets to be consumed	
		Intensive phase HRZE(4FDC) 75/150/400/275 mg per tablet	Continuation phase HRE(3FDC) 75/150/275 mg per tablet
Category-1 (New cases of Pulmonary and Extra-pulmonary)	25-34kg	2	2
	35-49kg	3	3
	50-64kg	4	4
	65-75kg	5	5
	>75kg	6	6

Data Sources: Sources of data collection included patient interview and patient RNTCP treatment card. Data sheets were prepared for 100 patients with informed consent forms. The details of age, sex, diagnosis, prescription data and adverse drug effects encountered were obtained from the case records.

Outcomes: Efficacy was assessed by sputum examination at 0, 2 and 6 months. CBNAAT assessment was used to make early and definitive diagnosis. X-rays and other special investigation relating to the specific type of EPTB were also analysed before and after treatment to monitor the efficacy. WHO-UMC causality assessment scale was used to assess the adverse drug reaction (ADR) reported during the study.

Sample Size: 100 patients, including both PTB and EPTB (Category-1) were taken up for the study. Finally, 96 treatment cards of patients were analysed due to drop outs.

.

Statistical Analysis: The cross tabulation was used to find out association between the parameters. Pearson Chi-square test and Fisher's exact test were used to find association between two groups. Data collected were entered in MS Excel and analysed with EPI INFO 3.5.4.

RESULTS

1.Morbidity distribution & Treatment outcome:**(Vide Fig 1 & Table 2)**

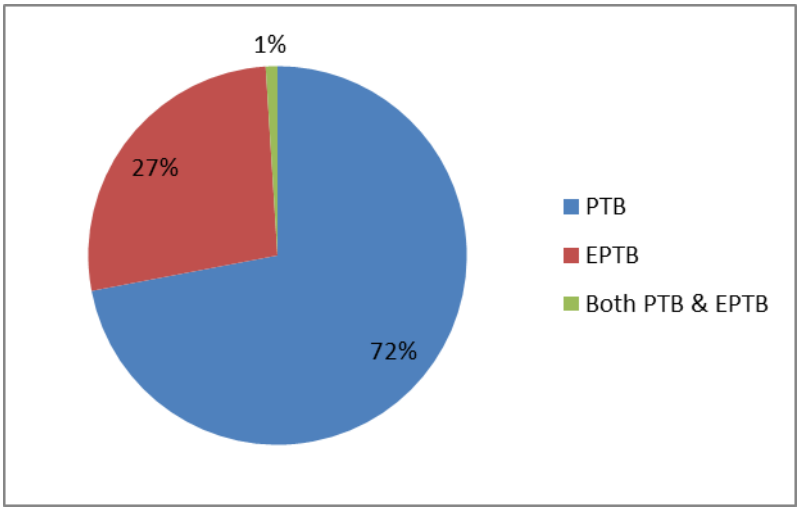
Among the 100 patients selected,

- 72 had PTB,
- 27 had EPTB and
- 1 was diagnosed with both PTB and EPTB, as illustrated in Fig 1.

Of the EPTB, 8 had pleural effusion, 14 lymphadenitis, 1 had ocular TB, 2 TB meningitis, 1 each diagnosed with TB spine and TB abdomen

Volume 3, Issue 3; May-June 2020; Page No.556-565

Fig1 Morbidity Distribution Pattern



Among the 100 patients, 95% completed the treatment, 4% were found to be drop-out and 1% was treatment failure. Out of the 4% drop out, 2% patients were PTB and 2% patients were EPTB, as observed in Table 2.

Table 2: Treatment outcome

Treatment	Diagnosis			p value
	PTB	EPTB	Both PTB & EPTB	
Completed	69	25	1	0.825
Failure	1	0	0	
Dropout	2	2	0	
Total	72	27	1	

2. Demographic data analysis: (Vide table 3 & Fig 2)

(i) Age wise distribution of patients: Among the study participants, 28% were in the age group 31 to 40 years, with PTB involvement more than EPTB as shown in Table 3.

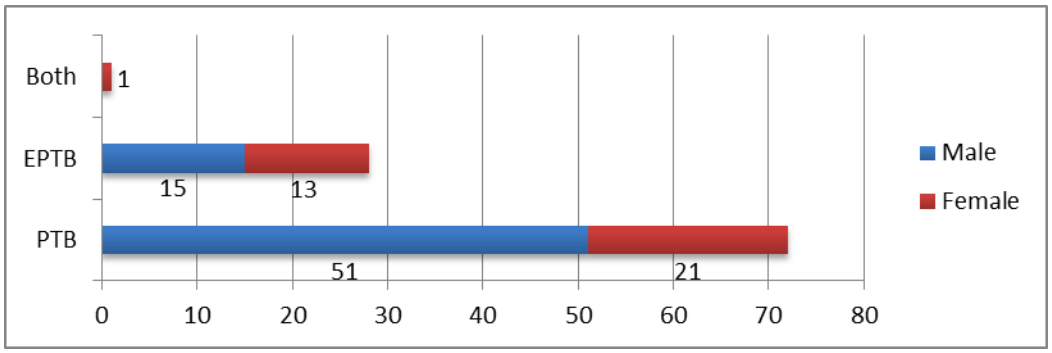
Table 3 – Age-wise distribution

DIAGNOSIS	AGE GROUP(In years)					p value
	13-20	21-30	31-40	41-50	51-60	
PTB	9	12	21	17	16	0.388
EPTB	8	6	6	3	5	
Both TB & EPTB	0	0	1	0	0	
Total	17	18	28	18	17	

Volume 3, Issue 3; May-June 2020; Page No.556-565

(ii) Gender wise distribution : Among the study participants, in fig 2, males were 66% and females were 34%. Among males, 47% were smokers and 62% were alcoholics contributing to social burden of the disease.

Fig 2: Gender wise distribution of disease pattern.



3. Efficacy analysis **(**Vide table 4)

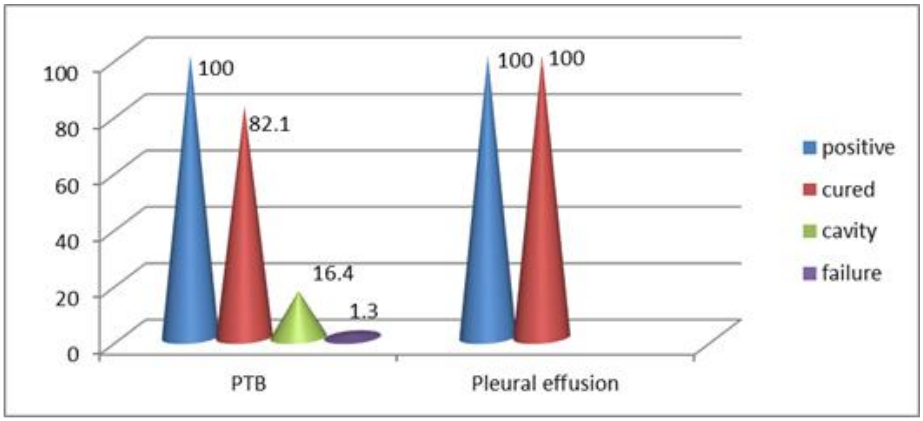
(i) Sputum for AFB: Among the 73 patients, 72 with PTB and 1 with both PTB & EPTB, 10.9% tested sputum negative but x-ray positive at diagnosis, 50.6% were (1+), 23.2% (2+) and 15% were (3+) respectively as depicted in Table 4. At the end of two months, 97.2% turned sputum negative, 1.3% remained (1+) and 1.3% remained (2+). At the end of 6 months, 98.5% turned sputum negative with failure of treatment in 1.4% of cases.

Table 4 Sputum AFB analysis

SPUTUM AFB	MONTHS			p value
	0	2	6	
0	8 (10.9%)	71 (97.2%)	70 (98.5%)	0.001
1+	37 (50.6%)	1 (1.3%)	0	
2+	17 (23.2%)	1 (1.3%)	1 (1.4%)	
3+	11 (15%)	0	0	

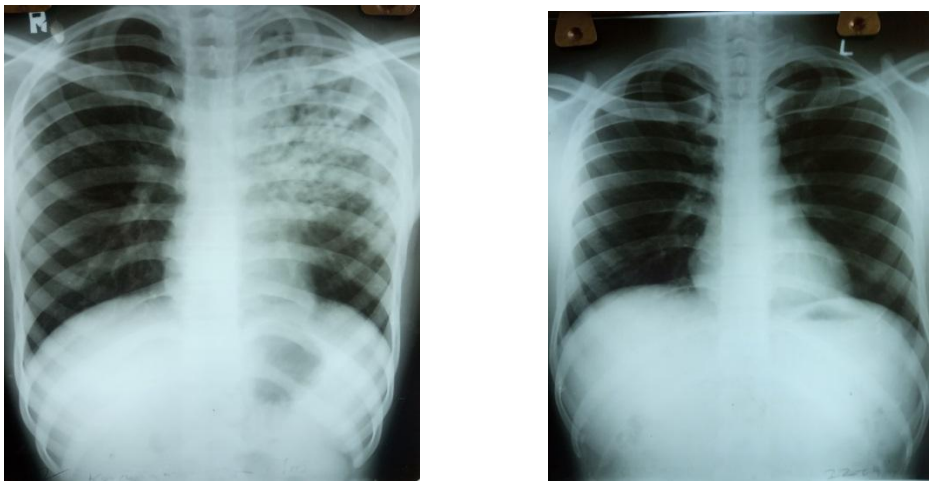
(ii) X-Ray: **(Vide Fig 3)** Among the 73 PTB cases, including 72 PTB and 1 PTB & EPTB , 82.1% patients cured, 1.3% showed failure of treatment while 16.4% were left with cavity. Among the 8 cases who were effusion positive, cure rate was 100% wherein effusion resolved completely in all cases.

Fig 3 X-Ray analysis in %



Volume 3, Issue 3; May-June 2020; Page No.556-565

Fig 4 X-Ray showing before and after treatment of Pulmonary TB



The x-rays in fig 4 shows improvement in x-ray findings after six months of treatment with Category-1 anti-tuberculosis drugs given as FDC.

CBNAAT (Vide table 5) was done for all patients who were diagnosed with TB, as an assessment of diagnostic sensitivity. But therapeutic outcome was not significant with this test because CBNAAT sensitises even the dead bacilli. Among 100 patients, CBNAAT was positive for all 100 cases, including 7 sputum negative cases.

Table 5: CBNAAT analysis

DIAGNOSIS	0 MONTHS	
	POSITIVE	NEGATIVE
Pulmonary TB	72	0
Pleural effusion	8	0
Lymphadenitis	14	0
Ocular TB	1	0
TB meningitis	2	0
TB spine	1	0
TB abdomen	1	0
Both pulmonary & extra pulmonary	1	0
TOTAL	100	0

Volume 3, Issue 3; May-June 2020; Page No.556-565

(iii) Other investigations (Vide table 6)

For EPTB, FNAC was done for 15 lymphadenitis patients, including 14 with TB lymphadenitis and 1 with both PTB and EPTB. This lymphadenitis was found to resolve completely after 6 months of drug therapy. Retinoscopy was done for 1 ocular TB patient which resolved completely at the end of 6 months. CSF examination done for 2 patients with TB meningitis, was negative for TB at the end of 12 months. Ascitic fluid analysis done for 1 TB abdomen patient showed clinical improvement at the end of 6 months.

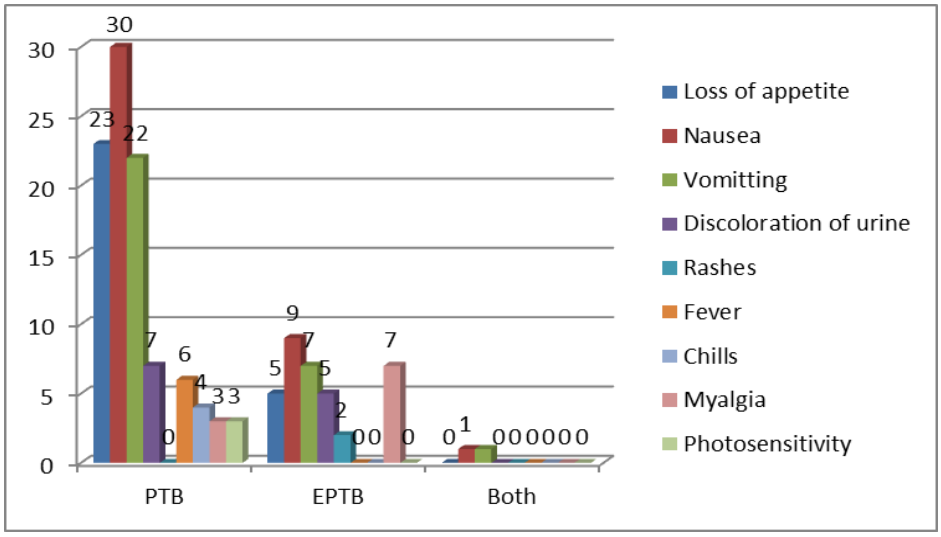
Table 6- Other investigations for EPTB

INVESTIGATIONS	BEFORE TREATMENT	AFTER TREATMENT
FNAC	15 positive	No swelling
Ocular- Retinoscopy	1 positive	1 negative
CSF examination	2 positive	2 negative
Ascitic fluid analysis	1 positive	1 negative

4. Adverse Effects (Vide Fig 5)

Among patients with PTB, 30% experienced nausea, 23% loss of appetite, 22% vomiting, 7% discoloration of urine, 1% rashes, 6% fever, 4% chills, 3% myalgia and 3% photosensitivity. In EPTB patients, 9% had nausea, 5% loss of appetite, 7% vomiting, 5% discoloration of urine, 2% had rashes and 7% had myalgia. In both PTB and EPTB cases, nausea and vomiting were frequently reported.

Fig 5 Adverse effects



DISCUSSION

The choice of effective anti-TB treatment is a major challenge since the discovery of disease. Use of FDC against tuberculosis is now being recommended to ensure optimal drug therapy. FDC simplifies the prescription of drugs and may help to limit the risk of drug-resistant tuberculosis[13] arising as a result of inappropriate drug selection and monotherapy.

From Fig 1, the observed incidence of lymphadenitis was most predominant with 15% of cases being EPTB. This multisystem disease leads to serious outcomes due to lack of proper investigations to diagnose the disease as well as

Volume 3, Issue 3; May-June 2020; Page No.556-565

access to adequate treatment measures. In the present study (vide table 6) patients with lymphadenitis, ocular TB, TB meningitis, TB abdomen who received drugs as FDC showed a more rapid clinical improvement. This improved efficacy of FDC observed in our study and also the decreased failure rates noted are in accordance with the study by Ayed et al.[14]

In our study, sputum conversion for PTB at the end of 6 months was 98.5% (Vide Table 4), which shows that there is an increased cure rate when the drugs were given in combination than separately. The effect was more pronounced in patients with sputum AFB (3+), where there was higher rate of clinical improvement and sputum negativity at the end of six months. This is similar to study conducted by Al-Shaer MH et al [15] where FDC showed faster smear conversion compared to standard regimen.

Previously, TB diagnosis was based entirely on sputum analysis and x-ray. But this was insufficient to detect the disease in sputum negative but x-ray positive cases. CBNAAT is a rapid molecular assay that helps to detect *M.tuberculosis* and Rifampicin resistance. The test is fully automated and provides results within 2 hours. It is mainly used in PTB patients who are smear negative but X-ray positive and EPTB patients to evaluate drug resistance.[16] CBNAAT analysis(Vide table 5) was used to increase the accuracy of diagnosis which correlates with the study conducted by Youngs J et al.[17] All the patients included in our study were sensitive to Rifampicin.

In the present study, X-ray results in Fig 3 indicated a cure rate of 82.1% , with treatment failure in 1.3% and 16.4% who were left with a cavity. In case of EPTB, among 8 cases who were effusion positive, 100% were cured, with effusion completely resolving in 6 months. This shows that there is an increased cure rate with combination of drugs compared with that of standard regimen which is similar to the study conducted by Wu J-T et al.[18] However the incidence of 16.4% cavity observed in PTB patients persisting post treatment, was probably due to a lower bioavailability of Rifampicin in these patients. This effect in FDC is probably a secondary reaction of Rifampicin with Isoniazid catalysed by Ethambutol and Pyrazinamide, which leads to lower peak plasma concentration of Rifampicin.[19,20]

From table 3 & Fig 2, the maximum affected sex is male (66%) and the most affected age group is 31 – 40 years. As mentioned in TB India report 2019[21], males in the working age group were the most affected, accounting for 2/3 of case burden. There is evidence that women may be less likely than men to seek or access health care in many settings. Smoking and alcoholism remains the major risk factors for men, that not only increases the incidence but also the severity of disease.[22] In our study, 47% of men were smokers and 62% of men were alcoholics. In a meta analysis conducted by Simou E et al, [23] data evaluated showed that, for every 10-20 g daily alcohol intake, there was a 12% increase in TB risk. Nutritional status was another parameter gauged by significant loss of weight/ weight gain in the one year study period.

From table 2, we surmise that 95% had completed the treatment with 1% failure and a dropout rate of 4%. This data analysed was in accordance with TB India Report 2019,[21] showing that drug combinations reduces the pill burden thereby improving the compliance in patients and minimises the tendency to skip doses.

Adverse drug reactions are the inevitable price we pay for benefit of any drug therapy. It is also imperative to monitor and treat adverse drug reactions developed by the patients. In our study, among the adverse effects, (Vide Fig 5) nausea(30%) and loss of appetite(23%) were commonly reported by PTB patients while fever(9%) and myalgia(7%) were reported by EPTB patients. However, no patients required alteration in treatment due to adverse drug reaction / adverse drug event.

The WHO-UMC system has been developed in consultation with the National Centres participating in the Programme for International Drug Monitoring and is meant as a practical tool for the assessment of case reports. WHO-UMC causality relationship was "**possible**" for all the reported adverse drug reaction. The adverse

Volume 3, Issue 3; May-June 2020; Page No.556-565

effects noted by the present study correlates with Baig MS et al[24] and also with Lima GC et al[25], whose meta-analysis showed decreased incidence of gastrointestinal adverse effects when FDC was used in comparison to individual drugs.

Therefore, incorporating FDC in the RNTCP regimen seems to provide greater efficacy and safety as well as lowers the incidence of drug resistance. Studies conducted to assess efficacy of Rifampicin, Isoniazid with or without Pyrazinamide administered in FDC for daily or intermittent use, also showed that FDCs are generally well tolerated with improved efficacy and safety than those of separate formulations.[6,7,9]

Strength of the study is the low drop out rate while the limitation of the study is the relatively short term follow up.

CONCLUSION

The present study has scientifically validated the efficacy and safety of Category-1 anti-tuberculosis drugs given in FDC. Emergence of resistance was not observed in our short term study indicating a more efficient TB control with this regimen.

ACKNOWLEDGEMENT

I am thankful to my guide Professor Dr.Vanitha Samuel, M.D., Ph.D., Professor and Head, Department of Pharmacology and my co-guide, Professor Dr.K.Pandian, M.D., D.T.C.D.,Professor and Head, Department of TB & Chest, Rajah muthiah medical college and hospital, Chidambaram for their inspiration to take up this study and for guiding me through each and every step of this Research Work. I also thank Dr.P.Nirmala M.D., Ph.D., Professor, Department of Pharmacology, for giving useful suggestions and helping me complete this work successfully.

CONFLICT OF INTERESTS

The authors do not have any conflicts of interest regarding the publication of this paper.

REFERENCES

1. World Health Organization, Global Tuberculosis Report, 2019. Available from: https://apps.who.int/iris/bitstream/handle/10665/329368/9789241565714-eng.pdf
2. TB India Report 2015.Available from: https://tbcindia.gov.in/showfile.php?lid=3166
3. Blomberg B, Spinaci S, Fourie B, Laing R. The rationale for recommending fixed-dose combination tablets for treatment of tuberculosis. Bull World Health Organ. 2001;79(1):61-68.
4. Technical and Operational Guidelines for TB Control in India,2016. Available from: https://tbcindia.gov.in/WriteReadData/l892s/8337437943TOG-Chapter%204-Treatment%20of%20TB%20Part%201.pdf
5. TB India Report 2018. Available from: https://tbcindia.gov.in/WriteReadData/TB%20India%202017.pdf
6. Nunn AJ ,Cook SV, Burgos M, Rigouts L, Edwards VY, Anyo G et al. Results at 30 months of a randomised trial of FDCs and separate drugs for the treatment of tuberculosis. Int J Tuberc Lung Dis. 2014;18(10):1252-1254.
7. Lienhardt C, Cook SV, Burgos M, Yorke-Edwards V, Rigouts L, Anyo G, et al. Efficacy and safety of a 4-drug fixed-dose combination regimen compared with separate drugs for treatment of pulmonary tuberculosis: the study C randomized controlled trial. JAMA.2011;305:1415–23.
8. Aseffa A, Chukwu JN, Vahedi M, Aguwa EN, Bedru A, Mebrahtu T, et al. Efficacy and safety of ‘fixed dose’ versus ‘loose’ drug regimens for treatment of pulmonary tuberculosis in two high TB burden African countries: a randomized controlled trial. PLoSOne.2016;11:e0157434.
9. Monedero I, Caminero JA. Evidence for promoting fixed dose combination drugs in tuberculosis treatment and control: A review. Int J Tuberc Lung Dis 2011;15:433-9.
10. The Importance of Pharmacovigilance, WHO 2002. Available from: https://www.who.int/medicines/areas/quality_safety/safety_efficacy/pharmvigi/en/

Volume 3, Issue 3; May-June 2020; Page No.556-565

11. Kapadia JD, Desai CK, Solanki MN, Shah AN, Dikshit RK. Efficacy and safety of anti-tuberculosis drugs in HIV-positive patients: a prospective study. Indian J Pharmacol. 2013 Sep-Oct;45(5):447-52.

12. Gholami K, Kamali E, Hajiabdolbaghi M, Shalviri G. Evaluation of anti-tuberculosis induced adverse reactions in hospitalized patients. Pharm Pract (Granada). 2006;4(3):134-8.

13. Chaudhuri AD. Recent changes in technical and operational guidelines for tuberculosis control programme in India - 2016: A paradigm shift in tuberculosis control. J Assoc Chest Physicians 2017;5:1-9.

14. Ayed H B, Koubaa M,Rekik K, Marrakchi C.Safety and Disease Evolution of Fixed-Dose Combination of Antitubercular Treatment Compared to Separate-Drugs Preparation in Extra-Pulmonary Tuberculosis.Current Pharmacology reports.2018;4(6):415-421

15. Al-Shaer MH, Mansour H, Elewa H, Salameh P, Iqbal F. Treatment outcomes of fixed-dose combination versus separate tablet regimens in pulmonary tuberculosis patients with or without diabetes in Qatar. BMC Infect Dis. 2017;17:118.

16. TB India Report 2017.Available from: https://tbcindia.gov.in/WriteReadData/TB%20India%202017.pdf

17. Youngs J, Patil S, Jain Y. A prospective study evaluating the impact of cartridge-based nucleic acid amplification test (CBNAAT) on the management of tuberculosis in a low-resource high-burden Indian rural setting. J Family Med Prim Care. 2018 Sep-Oct;7(5):982-992.

18. Wu J-T, Chiu C-T, Wei Y-F, Lai Y-F. Comparison of the safety and efficacy of a fixed-dose combination regimen and separate formulations for pulmonary tuberculosis treatment. Clinics. 2015;70:429–34.

19. Bhutani H, Singh S, Jindal KC, Chakraborti AK. Mechanistic explanation to the catalysis by pyrazinamide and ethambutol of reaction between rifampicin and isoniazid in anti-TB FDCs. J Pharm Biomed Anal 2005; 39:892–899.

20. El-Kholy Maha M, Sadek Samiaa H, Mahran Osama. Fixed-dose combination versus separate drug formula for pulmonary and extrapulmonary tuberculosis. Egypt J Bronchol 2018; 12(3):346–351

21. TB India Report 2019. Available from: https://tbcindia.gov.in/WriteReadData/India%20TB%20Report%202019.pdf

22. Thomas B.E., Thiruvengadam K., Kadam D S.R., Ovung S., Sivakumar S. Smoking, alcohol use disorder and tuberculosis treatment outcomes: a dual co-morbidity burden that cannot be ignored. PLoS One. 2019;14(7)

23. Simou E, Britton J, Leonardi-Bee J. Alcohol consumption and risk of tuberculosis: a systematic review and meta-analysis. Int J Tuberc Lung Dis. 2018;22(11):1277-1285.

24. Baig MS, Kale MR, Lamb A.A prospective observational pharmacovigilance study of adverse drug reaction monitoring in patients of MDR - TB at tertiary care hospital.IJBCP 2013;7(7):1291-1296

25. Lima GC, Silva EV, Magalhães PO, Naves JS. Efficacy and safety of a four-drug fixed-dose combination regimen versus separate drugs for treatment of pulmonary tuberculosis: a systematic review and meta-analysis. Braz J Microbiol. 2017;48(2):198–207

Volume 3, Issue 3; May-June 2020; Page No.556-565