Treatment outcome of drug resistant tuberculosis after 6 months of bedaquiline containing anti-tubercular treatment

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Abstract:

Background & Method: The aim is to study the treatment outcome of drug resistant tuberculosis after 6 months of bedaquiline containing anti-tubercular treatment. This study was conducted on patients enrolled under Nodal drug resistant tuberculosis centre or attending OPD in Department of Respiratory Medicine at Pt. J. N. M. Medical college, Raipur (C.G.) during study period. The institute provides NTEP, Nodal DR-TB centre and PMDT services, tertiary level of respiratory and critical care services to the patients. Inclusion/exclusion criteria and treatment initiation/follow up was done under programmatic guidelines. This study was performed primarily focusing on clinical profile and drug resistance pattern of patients to determine the treatment outcome after 6 months of bedaquiline-containing anti-tubercular regimen in DR-TB patients.

Result: Among all enrolled patients (n=38) 27 (71.1%) were undernourished, 10 (26.3%) were normal and 1(2.6%) patient was pre-obese. Mean BMI ($\pm$ standard deviation) was 16.71 ($\pm$ 2.74) Kg/m2. Out of 38 patients, 21(55.3%) patients were detected RIF Resistance by **NAAT**, 27(71.1%) patients had mutation in **Rpo-B** gene, 21(55.3%) patients had mutation in **Kat G** gene, 5(13.2%) patients had mutation in **Inh A**, 14(36.8%) patients had mutation in **Gyr A**, 0(0.0%) patients had mutation in **Gyr B** & **eis** genes, and 2(5.3%) patients had mutation in rrs gene. The rate of sputum smear and culture conversion at 3rd month were **83.33%** and **86.1%** and at 6th months were **88.8%** and **88.9%** respectively, 3 patients were died during the course of treatment and 2 patients were lost to follow-up.

Conclusion: This study concluded that bedaquiline is one of the most important component of the antitubercular regimen for drug resistant tuberculosis. It makes the anti-tubercular regimen more effective which leads to increased chance of sputum smear and culture conversion among DRTB patients. Bedaquiline is tolerated by most of the patient if started after following the programmatic management of drug resistant tuberculosis guidelines accordingly. Nutrition plays an important role in compliance of the patients. Higher rate of sputum smear and culture conversion helps not only in better cure of the patient but also helps in curtailing the spread of infection.

Keywords: drug, resistant, tuberculosis, bedaquiline & anti-tubercular.

Study Designed: Prospective Observational Study.

INTRODUCTION

Tuberculosis is a notorious infectious disease of mankind since ancient times. Its causative organism was first time identified on 24 March 1882, by Dr Robert Koch, who discovered this bacillus, & subsequently named as Mycobacterium tuberculosis.[1] About a quarter of the world's population are infected with Mycobacterium tuberculosis & among these, the lifetime risk of developing tuberculosis is about 5–10%. Tuberculosis is one of the leading cause of death from a single infectious agent (ranking above HIV/AIDS)[2].

Mycobacterium tuberculosis is a slow-growing mycobacterium with a doubling time of 12-24 hours under optimal conditions. The most important feature of this bacilli is its peculiar cell wall structure, which provides an exceptionally strong and impermeable barrier to noxious compounds and drugs and that plays a fundamental role in virulence and drug resistance[3].

Without treatment, the mortality rate from TB is very high. Studies of the natural history of tuberculosis disease in the absence of treatment with anti-tubercular drugs conducted before the antibiotic era, found that about 70% of individuals with sputum smear-positive pulmonary tuberculosis cases died within 10 years of being diagnosed.[4]

Microbiologically confirmed pulmonary tuberculosis cases are the most important source of infection and the droplet nuclei, mainly generated by coughing and sneezing, inhaled via the respiratory route, are the most common mode of getting infected. After infection when tubercular bacilli reach the alveoli of the host, phagocytized by alveolar macrophages & mostly get killed but when few bacilli become able to get survived, they start active multiplication in macrophages and diffuse into nearby cells including epithelial and endothelial cells, reaching in few weeks of exponential growth, a high bacterial burden, leads to pulmonary tuberculosis. The bacilli can diffuse into other organs via lymphatics and haematogenous dissemination where it can infect other cells & leads to extra-pulmonary tuberculosis.[5]

Screening of drug-resistant tuberculosis:
Presumptive DR-TB refers to the patient who is eligible for Rifampicin-resistant screening at the time of diagnosis or/and during treatment for DS TB or H mono/poly resistant tuberculosis. This includes all Notified TB patients, follow-up positive on microscopy including treatment failures on standard first-line treatment and all oral H mono/poly regimens and any clinical non-responder including paediatric (if specimen available)[6]
A presumptive case of MDR-TB is defined as a TB patient who fails a new treatment regimen and retreatment regimens with first-line anti-TB drugs who are sputum smear positive at the end of the 4th month of treatment or later and has close contact with drug-resistant TB cases.[6]

Diagnosis of drug-resistant tuberculosis:
The bacteriological evidence is the gold standard in the detection of MDR–TB/RR-TB. This is based on sputum smear microscopy, culture and drug resistance/susceptibility testing.[6]
Under programmatic management of drug-resistant tuberculosis in India guidelines (PMDT) 2021, all presumptive tuberculosis patients, key populations and diagnosed cases must undergo Universal Drug Sensitivity Testing or UDST.

Material & Method
This study was conducted on patients enrolled under nodal drug resistant tuberculosis centre or attending OPD in department of Respiratory medicine at Pt. J. N. M. Medical college, Raipur (C.G.) during study period. The institute provides NTEP, PMDT services, tertiary level of respiratory and critical care services to the patients. This study was performed primarily focusing on clinical profile and drug resistance pattern of patients to determine the treatment outcome after 6 months of bedaquiline-containing anti-tubercular regimen in DR-TB patients under programmatic conditions as per PMDT march 2021.

Inclusion criteria:
All patients with more than or equal to 18 years of age with confirmed case of drug resistant tuberculosis based on culture and drug sensitivity testing of biological specimen, who are eligible for bedaquiline-containing anti-tubercular regimen.
Exclusion criteria:
1.   Patients who are not willing in take part of study at any time during study.

2.   Patients who are found not qualified after pre-treatment evaluation as per PMDT
         guidelines march 2021.

Description of study:
This study was done on patients with confirmed cases of DR-PTB and eligible for bedaquiline-containing anti-tubercular regimen as per current PMDT guidelines enrolled or attending OPD of Department of Respiratory Medicine at Pt. J.N.M. medical college, Raipur (C.G.) during the study period. A total 38 patients of DR-PTB cases were enrolled in this study.
The study was proposed to be conducted after obtaining informed signed consent from the patients. All patients were explained about the details of study in their own languages. After obtaining informed signed consent from the patients to participate in the study, collects their baseline clinical detail including history, physical examination, and laboratory examinations as per norms of PMDT guidelines 2021 and after pre-treatment evaluation bedaquiline containing anti-tubercular regimen was started and then discharged as per guidelines. All enrolled patients were followed up for their compliance, adverse events and treatment outcome at 3rd and 6th months under programmatic conditions.

Results:

TABLE 1: DISTRIBUTION OF AGE

Age in Years	Frequency	Percentage
18-29	13	34.2
30-45	16	42.1
>46	9	23.7
Total	38	100.0

TABLE 2: DISTRIBUTION OF BODY MASS INDEX (BMI)

BMI in Kg/m²	Frequency	Percentage
Underweight <18.5	27	71.1
Normal 18.5-24.9	10	26.3
Pre-obese 25-29.9	01	2.6
Total	38	100.0

TABLE 3: ANTI-TUBERCULAR HISTORY

Age groups (in years)	Anti-tubercular history	
	YES	NO
18-29 %	9 (69.3%)	4(30.7%)
30-45 %	6 (37.5%)	10 (62.5%)
>45%	5 (55.6%)	4 (44.4%)

TABLE 4: DRUG RESISTANCE PATTERN

DRUG RESISTANCE PATTERN (n=38)	
NAAT (RR)	21(55.3%)
Rpo B	27(71.1%)
Kat G	21(55.3%)
Inh A	5(13.2%)
Gyr A	14(36.8%)
Gyr B	0(0.00%)
rrs	02(5.3%)
eis	0(0.00%)

TABLE 5: TREATMENT OUTCOME

RESULTS	SPUTUM SMEAR		CULTURE CONVERSION	
	At 3rd month	At 6th month	At 3rd month	At 6th month
Negative	30 (83.33%)	32 (88.8%)	31 (86.1%)	32 (88.9%)
Positive	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Contaminated	0 (0.00%)	0 (0.00%)	3 (8.3%)	1 (2.8%)
Not available	6 (16.66%)	4 (11.11%)	2 (5.6%)	3 (8.3%)

DISCUSSION:

The national strategic plan for TB 2020-2025, which replace and refresh the national strategic plan for TB 2017-2025, aim to eliminate tuberculosis in India by 2025. Drug resistant tuberculosis is a major obstacle in elimination of tuberculosis in India & across the world. Drug resistant tuberculosis not only add difficulty in treating the patients in terms of suffering from disease & compliance of anti-tubercular drugs, it significantly affects the quality of life of all DR-TB patients & their family members. It also affects socio-economic status, which can lead to add more medical co-morbidity to patients and their family members.

The only way to overcome these obstacle is to early diagnose the DR-TB cases, early start of most appropriate anti-tubercular regimen and continuous follow up and support the patient for better compliance till favourable outcome. In India programmatic management of drug resistant tuberculosis (PMDT) programme was introduced in 2007 and complete geographical coverage was achieved by year 2013. The bedaquiline was introduced as a part of anti-tubercular regimen for drug resistant tuberculosis cases in 2016 through conditional access programme (CAP) under RNTCP.

In our study all patients (100%) were rifampicin resistant, 63.15% patients were resistant to isoniazid also, 36.84% patients were fluoroquinolone resistant, 5.26% patients were resistant to second line injectable (SLI), 60.52% patients with both rifampicin & isoniazid resistant, 31.5% patients with both rifampicin and fluoroquinolone resistant and 5.2% patients with all three (rifampicin, fluoroquinolones and SLI) resistant. *Sarin R. et al*[7] were included 73.8% patients with both rifampicin and fluoroquinolone resistant and 4.8% with both rifampicin and second line injectable resistant and 20.7% patients with all three (rifampicin + fluoroquinolones

+ SLI) resistant. **Barvalia S. et al**[8] were enrolled all patients (100%) with rifampicin + isoniazid resistant followed by 91.3% patients with fluoroquinolones also. **Diacon A et al**[9] were included 76% patients with resistant to both rifampicin and isoniazid followed by 9% patients with fluoroquinolone resistant and 15% patients with SLI resistant.

In our study rate of sputum smear conversion at the end of 3rd month was 83.33% and at the end of 6th month was 88.8%, rate of culture conversion at the end of 3rd month was 86.1% and at the end of 6th month was 88.9%. 7.89% patient were died during the course of study and 5.26% patient were declared as lost to follow up. **Sarin R. et al**[7] were reported 93.4% and 97.9% patients had culture conversion at the end of the 3rd and 6th month respectively. **Borisov S. et al**[10] were reported sputum smear and culture conversion at 3rd month were 85.5% and 80.5% and at 6th month were 88.7% and 91.2% respectively. **Guglielmetti L. et al**[11,12] were reported 56.1% and 97.6% patients achieved culture conversion at 3rd and 6th month respectively. **Barvaliya S. et al**[8] were reported that 82.4% patients become culture negative at end of 6 months.

CONCLUSION

This study concluded that bedaquiline is one of the most important component of the antitubercular regimen for drug resistant tuberculosis. It makes the anti-tubercular regimen more effective which leads to increased chance of sputum smear and culture conversion among DRTB patients. Bedaquiline is tolerated by most of the patient if started after following the programmatic management of drug resistant tuberculosis guidelines accordingly. Nutrition plays an important role in compliance of the patients. Higher rate of sputum smear and culture conversion helps not only in better cure of the patient but also helps in curtailing the spread of infection.

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