ORIGINAL RESEARCH PAPER
Volume - 11 | Issue - 09 | September - 2022 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

COMPARATIVE STUDY OF BEDAQUILINE AND NON BEDAQUILINE REGIMEN IN MDR TUBERCULOSIS

Medicine

Dr Abilesh Kumar Associate Professor medicine JLNMCH BHAGALPUR.
Dr Pandu Azmeera Medicine Pg Resident JLNMCH BHAGALPUR.
Dr Ajitesh Kumar Medicine Pg Resident JLNMCH BHAGALPUR.
Dr Nalin Kumar Medicine Pg Resident JLNMCH BHAGALPUR.

ABSTRACT

tuberculosis caused by a bacteria mycobacterium tuberculosis. It is prevalent in developing countries due to malnutrition, unhygienic condition, overcrowding, socioeconomic condition and lack of health education. Even patients who receive treatment not complete their full duration this leads to development of MDR and XDR tuberculosis. After decades of ongoing research two new drugs namely bed aquiline and delamanid come in existence. Treatment of MDR TB and XDR TB has proven so far to be long, expensive and difficult to manage and unfortunately its outcomes are suboptimal in most cohorts although XDR TB cases actually represent a relatively small proportion of all MDR TB cases (9%), there treatment and management are significantly more challenging both for clinician and national programs. **Methods-** PROSPECTIVE RANDOMIZED **Control Study Design.** Source of data patients admitted to the department of internal medicine Jawaharlal Nehru medical college and hospital Bhagalpur. Sample size 90 patients 60 treated by non-bed aquiline and 30 treated by bed aquiline. in all the selected patients detailed history and physical examination findings noted. The patients subjected to sputum examination, chest X-ray, and biochemical evaluation of tuberculosis for treatment outcome. Duration of study 2 and half years. Suitable statistical tools use for analysis of data. **Summary-** Tuberculosis is one of the most common infectious diseases associated with significant mortality and morbidity. There has been significant progress in the management of TB. However, despite these advances, India has the second highest burden of MDR-TB in the world after China with an estimated 99,000 new cases per year (WHO, 2010b) . MDR-TB is difficult to treat due to ineffectiveness of first line drugs and the decreased efficacy and increased adverse events associated with second line of treatment. Only 48% cases of MDR-TB are successfully treated which is low resulting in increased mortality and poor quality of life of these patients. There is a constant need for better drugs with novel mechanisms of action to treat MDR-TB effectively with lower chances of drug resistance. Thus, the study being undertaken to compare different treatment regimen using bedaquiline and other drugs.

KEYWORDS

INTRODUCTION

Tuberculosis (TB) is an airborne infectious disease caused by Mycobacterium tuberculosis, that has baffled not only the uncountable patients with its lingering infections, punctuated by storms of life-threatening episodes but also the physicians who battle to burn down this stubborn bacterial infection. [1] Despite of 90 years of vaccination and 60 years of chemotherapy, tuberculosis (TB) remains the world's leading cause of death from an infectious agent, exceeding human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS). The World Health Organization (WHO) estimates that there are about 10.4 million new cases and 1.8 million deaths from TB each year. One-third of these new cases (about 3 million) remain unknown to the health system, and many are not receiving proper treatment.

Tuberculosis is an infectious bacterial disease caused by *Mycobacterium tuberculosis* (Mtb), which is transmitted between humans through the respiratory route and most commonly affects the lungs but can damage any tissue. Only about 10 percent of individuals infected with Mtb progress to active TB disease within their lifetime; the remainder of persons infected successfully contain their infection. One of the challenges of TB is that the pathogen persists in many infected individuals in a latent state for many years and can be reactivated to cause disease. The risk of progression to TB disease after infection is highest soon after the initial infection and increases dramatically for persons co-infected with HIV/AIDS or other immune-compromising conditions.

Treatment of TB disease requires multiple drugs for many months. These long drug regimens are challenging for both patients and health care systems, especially in low- and middle-income countries (LMICs), where the disease burden often far outstrips local resources. In some areas, the incidence of drug-resistant TB, requiring even longer treatment regimens with drugs that are more expensive and difficult to tolerate, is increasing.

Treatment effectiveness has been eroded, however, by the evolution and transmission of multidrug-resistant tuberculosis. Treatment for MDR TB, which is defined as resistance to isoniazid and rifampicin (the two most effective TB drugs) is longer and requires more expensive and more toxic drugs. For most patients with MDR TB, the current regimens recommended by the WHO last 18–24 months, and treatment success rates are much lower, around 60 percent. The WHO now conditionally recommends using seven drugs to reduce the time of treatment to nine months for uncomplicated pulmonary disease (WHO 2016b). New drug combinations, for example, including bed aquiline or delaminid, which are thought to act on new molecular targets, are being introduced, but an ideal combination is likely several years away.

Patients who are effectively treated for tuberculosis usually show clinical response within 8–12 weeks, both subjectively (reduced cough, fatigue, fevers, and sweats; increased appetite) and objectively (sputum smear or culture conversion from positive to negative; weight gain) (WHO 2010). Failure to respond to treatment is typically due to poor drug quality, underdosing or malabsorption, nonadherence, drug resistance (which may broaden while on treatment), paradoxical reactions or immune reconstitution inflammatory syndrome (IRIS), adverse drug effects, or another disease process (bronchiectasis, malignancy, pneumoconiosis, autoimmune disease, or organ failure).

Bedaquiline is a new ant tuberculous drug belonging to the diarylquinoline class that efficiently inhibits the adenosine triphosphate synthase enzyme of *Mycobacterium tuberculosis*. Bedaquiline offers a new mechanism of anti-TB action by specifically inhibiting mycobacterial adenosine triphosphate (ATP) synthase. Bedaquiline treatment consisted of **400 mg once daily for 2 weeks followed by 200 mg three times weekly for 22 weeks** (1,2,5).

METHOD-

Ours is a prospective randomised control study design based on patients admitted for management of Pre-XDR and XDR TB in indoor departments of internal medicine and pulmonary medicine in JLNMCH Bhagalpur. Duration of study is 30 months. 90 Patients were selected of which 30 patients were treated with bed aquiline based regimen and 60 patients were treated with non-bed aquiline based regimen.

Selection of cases:
Inclusion criteria-

1. Patients above 18 years of age.
2. Newly diagnosed cases of Pre-XDR and XDR Tuberculosis.

Exclusion criteria

1. Patients aged <18 years of age.
2. Patients with previous administration of ATT.
3. Patients with Extra-Pulmonary Tuberculosis.
4. Patients with other infectious diseases.
5. Pregnancy.

AIMS AND OBJECTIVES-

to compare bed aquiline and non- bed aquiline based drug regimen in pre-XDR and XDR TB with regards to following points: clinical improvement in terms of fever disappearance, reduction in cough, sputum clearance, radiological Clearence, comparison of efficacy, adverse effects, failure rates, mortality rates.

Procedure-

Those agreeing to participate in the study were randomly divided into two groups, patients in one group were assigned Bed aquiline Based Regimen and the patients in the other group were given non-bed aquiline based regimen.

In all the selected patients detailed history and physical examination were noted. The patients were subjected to sputum examination for microscopy and culture, Gene X-pert mtb/RIF , DST, X-ray Chest PA view, ECG, CBC, TFT, LFT, KFT, Serum uric acid and biochemical evaluation of tuberculosis (for treatment outcome). Treatment plan was followed according to the regimen assigned. Patients were evaluated for sputum microscopy at monthly intervals, and by CXR PA view at 0,1,3 6,12,24 months.

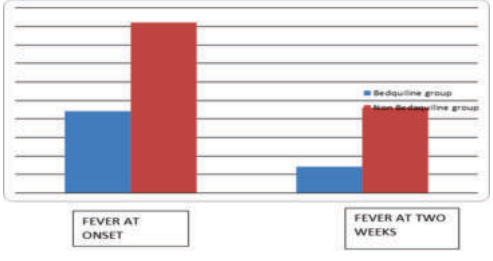
RESULTS AND ANALYSIS

The patients of both the groups were studied upon for all the clinical variables before the administration of Multi drug regimen and at different intervals during the course of therapy.

1) Fever

	Bedaquiline group	Non bedaquiline group	Total
Fever at onset	22/30=73.33%	46/60=76.66%	68/90
No fever at onset	8/30=26.67	14/60=23.34%	22/90
Total	30/30=100%	60/60=100%	90/90

	Bedaquiline group	Non bedaquiline group	Total
Fever at 2 weeks	7/30=23.33%	23/60=38.34%	30/90
No fever at 2 weeks	23/30= 76.67%	37/60=61.66%	60/90
Total	30	60	90



2) Cough Reduction

	BEDAQUILINE GROUP	NON-BEDAQUILINE GROUP	TOTAL
COUGH AT THE TIME OF ONSET	30/30= 100%	60/60= 100%	90/90
COUGH REDUCTION AT THE END OF ONE MONTH OF THERAPY	24/30= 80%	42/60= 70%	66/90
COUGH REDUCTION AT THE END OF TWO MONTH OF THERAPY	26/30= 86.66%	45/60= 75%	71/90

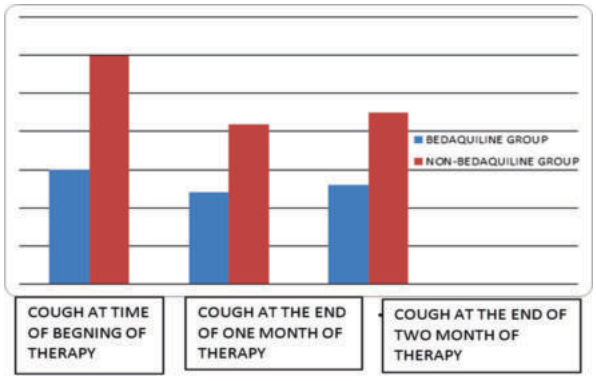
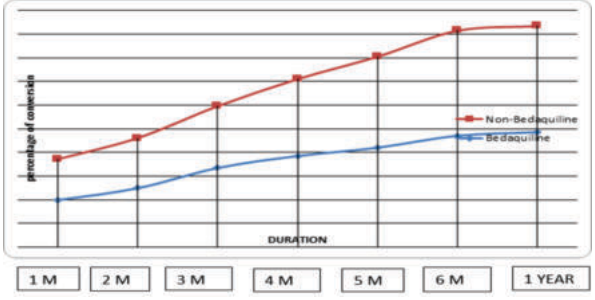


Figure 3: Cough reduction comparision in both the groups

3)Sputum Conversion

SPUTUM CULTURE RESULTS	BEDAQUILINE GROU	NON BEDAQUILINE GROUP	TOTAL
POSITIVE CASES AT BEGINNING	30/30= 100%	60/60= 100%	90/90
CONVERSION AT 1 MONTH	12/30= 40%	20/60= 33.33%	32/90
CONVERSION AT 2 MONTH	15/30=50%	25/60=41.66%	40/90
CONVERSION AT 3 MONTH	20/30=66.66%	31/60=51.66%	51/90
CONVERSION AT 4 MONTH	23/30=76.66%	39/60=65%	62/90
CONVERSION AT 5 MONTH	25/30=83.33%	46/60=76.66%	71/90
CONVERSION AT 6 MONTH	28/30= 93.33%	53/60= 88.33%	81/90
CONVERSION AT 1 YEAR	29/30=96.66%	54/60=90%	83/90

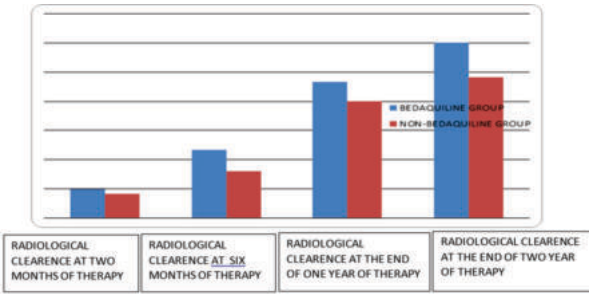


graph showing sputum conversion of both the groups.

4) Radiological Clearence

	BEDAQUILINE GROUP	NON BEDAQUILINE GROUP	TOTAL
RADIOLOGICAL ABNORMALITY AT THE BEGINNING OF THERAPY	30/30= 100%	60/60= 100%	90/90
RADIOLOGICAL CLEARENCE AT TWO MONTHS OF THERAPY	3/30= 10%	5/60= 8.3%	8/90
RADIOLOGICAL CLEARENCE AT SIX MONTHS OF THERAPY.	7/30= 23.33%	10/60= 16%	17/90
RADIOLOGICAL CLEARENCE AT ONE YEAR OF THERAPY.	14/30= 46.66%	24/60= 40%	38/90
RESIDUAL RADIOLOGICAL ABNORMALITY AT THE END OF ONE YEAR OF THERAPY.	16/30=53.33%	36/60=60%	52/90

RESIDUAL RADIOLOGICAL ABNORMALITY AT THE END OF TWO YEAR OF THERAPY.	12/30= 40%	31/60= 52%	43/90



5) Failure Rates

	BEDAQUILINE GROUP	NON-BEDAQUILINE GROUP
PATIENT ON ASSIGNED THERAPY	30/30= 100%	60/60=100%
FAILURE DUE TO ADVERSE EFFECT	1/30= 3%	1/60= 1.5%
DEFAULTER AT THE END OF THERAPY	1/30=3%	2/60=3%
NUMBER OF DEATHS AT THE END OF THERAPY	2/30=6.66%	5/60=8.3%
RELAPSE CASES	0/30=0%	2/60=3.33%
PATIENT CURED AT THE END OF THERAPY	26/30=86.66%	49/60=81.66%

P- Value Of Diffrent Study Variables:

Fever (Two Weeks Of Therapy) P-value 0.530.
Weight Gain (Two Months Of Therapy) P-value 0.683.
Cough Reduction (Two Months Of Therapy) P-value 0.664.
Sputum Conversion (Six Months Of Therapy) P-value 0.865.
Radiological Clearence (Six Months Of Therapy) P-value 0.533.
Cure Rate (At The End Of Therapy) P-value 0.814.
P- Value Was Not Significant Among All Study Variables.

DISCUSSION

Tuberculosis is one of the most infectious diseases associated with significant mortality and morbidity. There has been significant progress in the management of tuberculosis. Only 48% cases of MDR TB are successfully treated which is low resulting in preXDR and XDR TB, increased mortality and poor quality of life of these patients. There is a constant need for better drugs with novel mechanism of action to treat resistant TB cases effectively with lower chances of drug resistance.

Bedaquiline-

With the availability of novel drug BEDAQUILINE with different mechanism has revolutionized the therapy of preXDR and XDR TB . Bedaquiline is a first in class diaryl quinoline, binds to subunit C of mycobacterial ATP-synthase (An enzyme essential for the energy production in mycobacterium tuberculosis) and inhibits its activity. Its selectivity index more than 20,000 .(1,2,5). Bedaquiline drug was approved by US FDA for use in the treatment of drug resistent TB in 2012. Bedaquiline used in combination with 4 second line ATT drugs for a period of 24 weeks. In preXDR TB Bedaquiline used for a period of 6 to 9 months intensive phase along with second line drugs and Non-Bedaquiline drugs continued during countinuation phase for a period of 18 months. (total duration of therapy 24 to 27 months based on recovery and bacteriological conversion). In XDR TB Bedaquiline given for a period of 6 to 12 months during intensive phase and 18 months period of continuation phase with Non –Bedaquiline drugs (total duration of regimen 24 to 30 months.). The dose of bedaquiline is 400mg per day for two weeks than 200mg 3 times per week with at least 48 hour between doses from 3 week to 24 weeks. Bedaquiline uses associated with nausea, stomach pain, headache, skin rash, joint pain. Hepatic insufficiency with increased ALT, AST and ECG changes (QT prolongation, fast or irregular heart beat.) and 1 to 10% mortality risk. 73.33% patients of bedaquiline group had fever at the time of admission, while 76.66% of patients assigned to the non-bedaquiline group had fever at the time of admission.

After 2 weeks of treatment 76.67 % of patients in the Bedaquiline group were afebrile. While 61.66% of the patients in the Non-Bedaquiline arm were afebrile. 80% Of patients in the Bedaquiline group showed cough reduction by the end of the 1 monthg of therapy. 70% Of patients in the Non-Bedaquiline group showed cough reduction by the end of the 1 month of therapy. 86.66% Of patients in the Bedaquiline group showed cough reduction by the end of 2 months of therapy. 75% Of patients in the Non-Bedaquiline group showed cough reduction by the end of 2 months of therapy. 40% Of patients in the Bedaquiline group showed sputum conversion by the end of 1 month of therapy. 33.33% Of patients in the Non-Bedaquiline group showed sputum conversion by the end of 1 month of therapy. 50% Of patients in the Bedaquiline group showed sputum conversion by the end of 2 months of therapy. 41.66% Of patients in the Non-Bedaquiline group showed sputum conversion by the end of 2 months of therapy. 66.66% Of patients in the Bedaquiline group showed sputum conversion by the end of 3 months of therapy. 51.66% Of patients in the Non-Bedaquiline group showed sputum conversion by the end of 3 months of therapy. 76.66% of patients in the Bedaquiline group showed sputum conversion by the end of 4 months of therapy. 65% Of patients in the Non-Bedaquiline group showed sputum conversion by the end of 4 months of therapy. 83.33% Of patients in the Bedaquiline group showed sputum conversion by the end of 5 months of therapy. 76.66% Of patients in the Non-Bedaquiline group showed sputum conversion by the end of 5 months of therapy. 93.33% Of patients in the Bedaquiline group showed sputum conversion by the end of 6 months of therapy. 88.33% Of patients in Non-Bedaquiline group showed sputum conversion by the end of 6 months of therapy. 96.66% Of patients in the Bedaquiline group showed sputum conversion by the end of 1 year of therapy. 90% Of patients in the Non-Bedaquiline group showed sputum conversion by the end of 1 year of therapy. 10% Of patients assigned to the Bedaquiline group showed radiological clearance by the end of 2 months of therapy. 8.3% Of patients assigned to the Non-Bedaquiline group showed radiological clearance by the end of 2 months of therapy. 23.33% Of patients assigned to the Bedaquiline group showed radiological clearance by the end of 6 months of therapy. 16% of patients assigned to the Non-Bedaquiline group showed radiological clearance by the end of 6 months of therapy. 46.66% Of patients assigned to the Bedaquiline group showed radiological clearance by the end of 1 year of therapy. 40% Of patients assigned to the Non-Bedaquiline group showed radiological clearance by the end of 1 year of therapy. 53.33% Of patients assigned to the Bedaquiline group showed residual radiological abnormality by the end of 1 year of therapy. 60% Of patients assigned to the Non-Bedaquline group showed residual radiological abnormality by the end of 1 year of therapy. 60% Of patients assigned to the Bedaquiline group showed radiological clearance by the end of 2 years of therapy. 48% Of patients assigned to the Non-Bedaquiline group showed radiological clearance by the end of 2 years of therapy. 40% Of patients assigned to the Bedaquiline group showed residual radiological abnormality by the end of 2 years of therapy. 52% Of patients assigned to the Non-Bedaquiline group showed residual radiological abnormality by the end of 2 years of therapy. 3% Of patients in the Bedaquiline group developed drug **adverse effects** and stopped assigned therapy. 1.5% Of patients in the Non-Bedaquiline group developed **adverse effects.** 6.66% **Mortality** observed in patients assigned to the **Bedaquiline group.** 8.3% **Mortality** observed in patients assigned to the **Non-Bedaquiline group. No Relapse** cases found in **Bedaquiline group.** 3.33% **Relapse cases** found among patients assigned to the **Non-Bedaquiline group.** 86.66% Of patients assigned to the **Bedaquiline group** were **cured.** 81.66% Of patients assigned to the **Non-Bedaquiline** group were **cured**.

CONCLUSION

Tuberculosis, One of the oldest disease the mankind has witnessed still never fail to bewilder the medical fraternity. Despite of the havoc created by the Covid19 the tuberculosis still failed to get dethroned from the chair of being the most perplexing and intriguing disorders. Despite of all the researches and interventions Tuberculosis still hasn't got a pinpoint treatment to target against it. Amongst the array of treatment line ups and upcoming treatment protocols, two new drugs Bedaquiline and Delaminid have entered the frame of tuberculosis management after few decades. Our study design aimed to explore these two newly born drugs in the treatment of Pre-XDR and XDR tuberculosis. We compared the clinical improvements, sputum clearances, radiological clearances and safety profile of two groups of

patients having been given Bedaquiline or not. Our study was of conclusion in line with expert group recommendations of WHO. With a greater reduction in fever (76.67% vs 61.66%), greater reduction in cough (80% vs 70%) at one month of therapy, greater sputum conversion (40% vs 33.33%) at one month of therapy, greater radiological clearance at 6 months 23% vs 16% the Bedaquiline group fared better in all the parameters(2,3,4,5,6). But the Bedaquiline group had a higher incidence of adverse effect (3% vs 1.5%) which was statistically significant (2,5). Although most of the adverse events were minor and easily manageable, but few were irreparable and caused serious implications. Our study came to the conclusion that, while experience in the use of Bedaquiline in the management of XDR-TB is limited, it may have an indication in such patients given the limitations in designing an effective regimen based on existing recommendations in many situations. In patients resistant to both classes of injectable drugs and also to fluoroquinolones (i.e. XDR-TB), bedaquiline may lower the need to include drugs belonging to Group 5, some of which have unproven anti-TB activity, high cost, and/or high toxicity. Bedaquiline may thus be used with or instead of a Group 5 drug. In these cases, special caution is advised on the potential increase of adverse drug reactions due to potential drug-drug interactions, particularly the synergistic cardiotoxic effect on QT prolongation, necessitating close ECG monitoring. As data from many studies showing clinical improvement and mortality of about 48% but in our study mortality was 8.3% this huge disparity in data is due to small study. This needs larger study group for further comparison. The overall result from Bedaquiline group is far better as compared to non-bedaquiline group. By this study bedaquiline is a wonderful drug in comparison to previous standard protocol regimen.

REFERENCES

1. Journal of Global Antimicrobial Resistance Bedaquiline: Current status and future perspectives https://www.sciencedirect.com/science/article/pii/S2213716521000497
2. Bedaquiline and multidrug-resistant tuberculosis: a systematic and critical analysis of the evidence https://erj.ersjournals.com/content/47/2/394#:~
3. Efficacy of bedaquiline in the treatment of drug-resistant tuberculosis: a systematic review and meta-analysis https://bmcinfectdis.biomedcentral.com/articles/10.1 186/s12879-021-06666-8
4. Outcomes of Bedaquiline Treatment in Patients with Multidrug-Resistant Tuberculosis https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6478224/
5. Effectiveness and safety of bedaquiline-containing regimens in the treatment of MDR- and XDR-TB: a multicentre study. https://erj.ersjournals. com/content/ 49/5/ 1700387.
6. Culture Conversion in Patients Treated with Bedaquiline and/or Delamanid. A Prospective Multicountry Study https://www.atsjournals.org/doi/10.1164/rccm.202001-0135OC