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ORIGINAL RESEARCH

A Study of Bedaquiline-Containing Regimens for MDR and XDR-TB Treatment

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ABSTRACT

Introduction: Due to its protracted duration, toxicity, high expense, and unfavourable results, the treatment of multidrug-resistant (MDR)/extensively drug-resistant (XDR) tuberculosis (TB) has proven difficult during the past few decades.

Methods: A prospective study with 50 drug-resistant tuberculosis patients who are taking bedaquiline as part of a treatment regimen and who meet the requirements of being over 18 years old, all genders, and having biological samples that show drug resistance that has been confirmed by phenotypic or genetic testing.

Results: Nausea was the most frequent side effect, followed by diarrhoea, joint discomfort, anorexia, and itching. There was no hepatotoxic effect.

Conclusion: A regimen using bedaquiline produced positive results. The benefit clearly justifies the risk even though bedaquiline and concurrent anti-TB medicines have the potential to lengthen QTc interval.

INTRODUCTION

A recent report from the World Health Organization (WHO) predicted 484,000 new cases of rifampicin-resistant tuberculosis (RR-TB), of which 78% were multidrug-resistant cases (MDR-TB) [1]. A diarylquinoline anti-mycobacterial medication called bedaquiline (BDQ), a more recent therapy option for MDRTB, was authorised by the US Food and Drug Administration in 2012 [2]. It inhibits mycobacterial adenosine triphosphate (ATP) synthesis. The addition of BDQ to a typical anti-MDR-TB therapy regimen has been found to improve patient long-term survival [2-4], decrease the time to sputum culture conversion, and raise the proportion of patients with persistent negative sputum culture results. However, there are just a few recently published clinical studies on the use of BDQ in patients with pulmonary MDR-TB.

The biggest number of tuberculosis cases are still found in India. [5] According to the National Anti-TB Drug Resistance Survey for 2014-16, 28.02 percent of patients had drug resistance to any substance, including 6.19 percent MDR-TB patients and 1.3% XDR-TB. [6]

A new drug, Bedaquiline (BDQ), was given a special approval for "compassionate use" under strict active drug safety monitoring (Cohort event monitoring) by Apex Committee under Supreme Court of India in 2016. This was done in light of DR-TB, a disease of particular relevance to the Indian health scenario with a lack of effective therapy.

METHODS

50 patients in the TB and Chest Department participated in the prospective study. The investigation was carried out over the course of a full year. Patients over the age of 18 who have a biological specimen that demonstrates drug resistance to rifampicin and isoniazid that is either phenotypically or genotypically proven, with resistance to both drugs (XDR TB), or who have a history of prior failure with a shorter regimen {Mfx, Km, Eto, Cfz, H, E (4-6m) + Mfx, Cfz, E (5m), conventional regimen{Lfx, Km, Eto, Cs, Z, E (6-9m) + Lfx, Eto, Cs, E (18m)}, XDR regimen{Cm, PAS, Mfx, H, Cfz, Lzd, Amx/clv (6-12m) + PAS, Mfx, Cfz, Lzd, Amx/clav) (18m)} admitted for evaluation under DOTS PLUS DRTB centre of our institute. Pre-treatment evaluation was done according to PMDT guidelines. After obtaining their informed consent, they began a bedaquiline-containing regimen. Age, gender, place of residence, respiratory symptoms, family history of TB or exposure to TB patients with microbiologic confirmation, history of smoking, and alcoholism were all thoroughly recorded. Initial chest X-ray, daily evaluation of the patient for negative reactions, and two-week ECG monitoring were carried out. For a period of six months, the patient was followed up on monthly basis for evaluation of the patient's sputum conversion, liver function test, chest X-ray, ECG, and any other adverse drug responses. Patients with a history of unstable cardiac arrhythmia, those admitted to the Dots Plus centre for fewer than 14 days, those in poor general health, and patients who were pregnant or nursing were excluded from the trial. Data were entered into an excel spreadsheet for statistical analysis, which was then done using simple descriptive statistics with the help of pie charts, line graphs, and box and whisker plots.

RESULTS

50 MDR-TB patients in all were enrolled. Table 1 displays the patient characteristics. The majority of the patients were under 30 years old, had a low body mass index (BMI) of 18.5 kg/m^2, and had already received anti-TB medication.

Table 1- Baseline general characteristics of the MDR-TB patients in the study (n=50)

Parameter	MDR-TB patients on DST guided regimen
Mean Age	31.5
Gender	
Men	40
Women	10
Body Mass Index	
<18.5	37
18.6-24.9	12
>25	1
Personal Habits	
Smoking	13
Tobacco Chewing	6
Alcohol Consumption	3
Smoking+Tobacco	1
Tobacco+Alcohol	2
Smoking+Alcohol	1
No Habits	20
Family History of TB	4

Male patients made up the majority (40), while female patients made up only 10%. 49 percent of the patients were between the ages of 21 and 30 and came from rural areas; 76.25

percent were illiterate, and the majority of them were poor, with a B G Prasad level 5 education (per capita monthly income less than 985).

Table 2- Side effect profile of Bedaquiline

Side Effects	Number
Nausea	16
Diarrhoea	12
Joint pain	7
Anorexia	5
Itching	4
Tachycardia	3
Blackish Discolouration of skin	3

DISCUSSION

The most prevalent AEs in our study were comparable to those typically reported in MDR-TB therapy cohorts. The most common adverse reactions that were recorded were diarrhoea, nausea, joint discomfort, anorexia, itching, tachycardia, and darkening of the skin. The most frequent adverse events, according to Sergey E. Borisov et al. [7], were nausea (31.5 percent), otovestibular toxicity (23.3 percent), peripheral neuropathy (23.3 percent), vomiting (21.2 percent), anaemia (20.9 percent), and arthralgia (20.4%), with slightly lower frequencies than those noted in Diacon et al. study (41 percent nausea, 29 percent vomiting and 37 percent arthralgia) [8]. The proportions of adverse events in the study by Diacon et al. were comparable in the treatment group compared to placebo patients, indicating that they were likely caused by the background regimen [9].

Other second-line medications in this situation, like fluoroquinolones or clofazimine, could contribute to adverse cardiological or other outcomes, thus they should be used with caution and ECG monitoring. The findings of our investigation show that, generally speaking, compared to previously published regimens, those incorporating bedaquiline achieve a relatively larger proportion of successful treatments and a relatively lower proportion of adverse events. Our research has several restrictions. First of all, the sample size was constrained by the short time span. Second, we were unable to determine whether any anti-TB medications other than bedaquiline were responsible for the side effects.

A promising role for bedaquiline and linezolid is when fluoroquinolone-resistant strains are present. [10] Patients with MDR-TB who received treatment with a linezolid-containing regimen have reported having a high sputum culture conversion rate (>87 percent). [11,12] In fact, difficult MDR-TB and XDR-TB patients treated with BDQ showed sputum culture conversion rates of 97 percent. [13] More significantly, the median conversion time for sputum cultures was as quick as 40 days, which is in line with the literature that is already accessible. [14,15] As a result, the sputum culture conversion rate and time were higher and quicker in the BDQ-containing regimen. It can be said that DST-guided customised regimens with bedaquiline and extremely potent anti-TB medications significantly improved the therapeutic outcomes for study participants with DR-TB.

The WHO published its active TB drug safety monitoring and management (aDSM) framework in 2015, which outlined how to put active pharmacovigilance into practise in order to quickly identify, handle, and report suspected or confirmed drug toxicities in the context of new medications and brief treatment regimens. With treatment regimens containing BDQ and delamanid (DLM), the first worldwide study for surveillance of adverse event of 26 nations recently showed that aDSM was achievable and the overall proportion of AEs was quite low (8.7% of patients with serious AEs (grade 3 and 4, no grade 5 AEs) [16].

CONCLUSION

Early sputum smear and culture conversion is linked to bedaquiline-containing regimens, along with a number of minor side effects. It is tolerable and generally safe. Patients with MDR and XDR-TB may benefit from this as a therapy. Though they were seen in a small number of individuals, ECG abnormalities such QTcF prolongation and tachycardia did not have any fatal consequences. Over the course of bedaquiline-containing regimen medication for six months, there were no abnormalities in liver function tests.

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