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A STUDY ON ADVERSE DRUG REACTIONS OF BEDAQUILINE CONTAINING REGIMEN IN PATIENTS WITH DRUG RESISTANT TUBERCULOSIS.

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Abstract

Context: Newer drugs like Bedaquiline and Delamanid are expected to improve treatment outcomes among selected population. Bedaquiline has serious side effects include QT prolongation, liver dysfunction, and an increased risk of death.

Aims: Due to paucity of study on the adverse effects of Bedaquiline containing regimen we have conducted this study to find out the side effect profile of patients treated with Bedaquiline.

Settings and Design: A prospective study involving 55 patients of Drug Resistant TB on a regimen containing Bedaquiline fulfilling the criteria that they are above 18 years of age and all genders with biological specimen showing phenotypically or genotypically confirmed drug resistant tuberculosis.

Statistical Analysis Used: All data were entered in Microsoft Excel and appropriate simple descriptive statistical methods were used.

Results: Most common adverse effect was nausea followed by diarrhoea, joint pain , anorexia and itching. No hepatotoxic effect was found.

Conclusion: Bedaquiline containing regimen is associated with early sputum smear and culture conversion and is relatively safe and well tolerated with no derangement in liver function. This could be considered as an effective treatment for MDR and XDR patients.

Keywords: Adverse Drug Reactions, Antitubercular Agents, Drug-resistant tuberculosis

Key messages: Bedaquiline containing regimen is relatively safe and effective in treatment of drug resistant tuberculosis.

Introduction

Tuberculosis a multi systemic disease with a myriad of presentations and manifestations, is the most common cause of infectious disease-related mortality worldwide [1]. Currently the WHO estimated incidence of drug resistant tuberculosis in India is estimated to be around 147000. It means 11 patients per 100000 population annually as per the global Tb report 2017 [2].

Bedaquiline is used to treat multi-drug-resistant tuberculosis (MDR-TB) when other treatment modalities cannot be used. The drug has a high volume of distribution, undergoes hepatic metabolism and has an extended half-life, which means that is still present in the plasma up to 5.5 months post stopping Bedaquiline [3, 6].

Common side effects include nausea, joint pains, headaches, and chest pain [4]. Serious side effects include QT prolongation, liver dysfunction, and an increased risk of death [4, 5].

Very few studies have been conducted in Eastern India regarding the side effect profile of Bedaquiline containing regimen in treatment of Drug Resistant TB, hence this study was conducted to study the side effect profile of Bedaquiline containing regimen in DRTB patients.

Subjects and Methods:

The study was a prospective study conducted among 55 patients attending Respiratory Medicine Department. The study was conducted for a period of one year. Patients of more than 18 years of age with biological specimen showing phenotypically or genotypically confirmed drug resistant tuberculosis with resistance to Rifampicin and Isoniazid with either FQ or SLID resistance (pre-XDR) or both (XDR TB) or with a history of previous history of failure of 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 taking informed consent they were started on regimen containing Bedaquiline. Detailed history as to age, gender, residence, respiratory symptoms, family history of TB or exposure to microbiologically confirmed TB patients, history of smoking and alcoholism were taken. Initial Chest X-Ray, daily assessment of patient for adverse reactions and ECG monitoring for two weeks was done. Patient was followed up monthly for evaluation of sputum conversion, liver function test, Chest X-Ray, ECG and any

other adverse drug reactions for a 6-month period. Patients having history of unstable cardiac arrhythmia, admitted for less than 14 days in Dots Plus center, poor general condition, pregnant and lactating patients were excluded from the study. Statistical analysis was done by entering data in excel sheet and analysed by simple descriptive statistics using Pie Chart, Line Graph and Box and Whisker plot.

Results:

Majority of patients were male (41) and female (14) with ratio of 3:1 as seen in **Figure 1**.

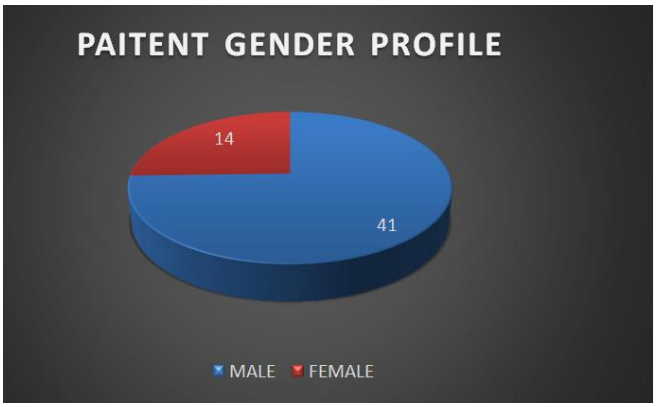

Figure 1: Gender Profile:

Most of the patients were in the age group of 21 to 30 years (49%) as can be seen in **Figure 2**. 92.72% were from rural areas, 76.25% were illiterate and most of them were poor with B G Prasad class 5 (per capita monthly income less than 985)**.**

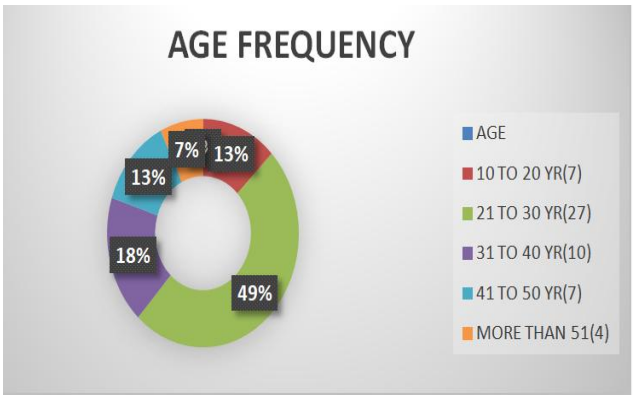

Figure 2: Age Frequency:

Table 1: Side effect profile of Bedaquiline:

Side effects	Number(%)
Nausea	**12(21.8)**
Diarrhoea	**11(20)**
Joint pain	**7(12.7)**
Anorexia	**3(5.3)**
Itching	**5(9)**
Tachycardia	**3(5.3)**
Blackish discolouration of skin	**4(7.2)**

Discussion:

In our study the most common AEs were similar to those frequently described in treatment cohorts with MDR-TB. The majority of the adverse events reported were nausea, diarrhoea, joint pain, anorexia, itching, tachycardia, blackish skin discolouration. Sergey E. Borisov et.al. [10] reported the most frequent adverse events as nausea (31.5%), otovestibular toxicity (23.3%), peripheral neuropathy (23.3%), vomiting (21.2%), anaemia (20.9%) and arthralgia (20.4%), their frequencies being slightly lower than those described during the licensing study by Diacon et al. (41% nausea, 29% vomiting and 37% arthralgia) [4]. Importantly, in the study by Diacon et al. the proportions of adverse events were similar in the treatment group versus placebo patients, suggesting that they were probably due to the background regimen [7]. In this context, other second-line drugs such as fluoroquinolones or clofazimine might contribute to cardiological or other adverse events, and invite caution and ECG monitoring. The results of our study demonstrate that overall, Bedaquiline-containing regimens achieve a relatively higher proportion of treatment success with a relatively lower proportion of adverse events within different settings than previously described. Our study had a few limitations. Firstly, the sample size was limited due to limited time frame. Secondly, we couldn't conclude if other anti TB drugs contributed to the adverse effects apart from Bedaquiline.

Conclusion:

Bedaquiline containing regimen is associated with early sputum smear and culture conversion and several non-serious adverse events. It is relatively safe and well tolerated. This could be considered as an effective treatment for MDR and XDR TB patients. ECG findings such as QTcF prolongation and tachycardia were observed in a few patients, though they did not cause any fatal outcome. There were no derangements in liver function tests over the period 6 months of Bedaquiline containing regimen therapy. Further large-scale studies are recommended with a closer look on the safety issues. In our study, success rates and cure rates are higher compared to other studies while death rates and failure rates are less compared to other studies. Hence, we can conclude that Bedaquiline containing regimen is safe and effective which is very useful in treatment of Drug Resistant TB,

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