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Original Research Paper

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A STUDY OF ANALYSIS OF VARIOUS ADVERSE DRUG REACTIONS (ADRS) IN PATIENTS OF DRUG RESISTANT TUBERCULOSIS (DR TB) ON BEDAQUILINE REGIMEN

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ABSTRACT

BACKGROUND: Adverse drug reactions (ADRs) are one of the main challenge in the treatment of Multi-drug resistant tuberculosis (MDR-TB). Patients may not take treatment if ADRs are not properly accessed and patients may stop taking drugs resulting in treatment failure.It is essential to monitor adverse drug effects in a systematic and timely manner.

METHODS: Patients receiving MDR-TB treatment as BDQ regimen in DR-TB Centre of AMC MET Medical college during the period of August 2020 to January 2021 are taken into study. Data of patients for the complaints of ADR is collected from patients.

RESULTS: Out of 100 patients, 55 patients (55%) experienced ADR. Among 55 reported ADRs, Gastrointestinal upset (nausea, vomiting) is the most common ADR reported (42%) followed by Hepatitis(22%),Peripheral neuropathy(11%), QTC prolongation (09%), Hypomagnesemia(5.5%), Redness of skin (5.5%), Optic neuropathy(04%) and Psychosis (02%).

CONCLUSION: GI upset, QT prolongation and peripheral neuropathy are major concerns in the successful management of MDR-TB with Bedaquiline containing regimen as they commonly lead to drug withdrawal, poor patient compliance and use of less efficient drugs in the regimen. Therefore the patients and their relatives and health workers should be aware of these ADRs for early detection and treatment.

KEYWORDS : ADR, Drug resistance, Bedaquiline regimen, MDR-TB, Tuberculosis

INTRODUCTION:

MDR-TB is defined as patient whose biological specimen is resistant to both H and R with or without resistance to other first line anti-TB drugs[1]. Adverse drug reactions (ADRs) are one of the main challenge in the treatment of Multi-drug resistant tuberculosis (MDR-TB). Patients may not take treatment if ADRs are not properly accessed and patients may stop taking drugs resulting in treatment failure. It is essential to monitor adverse drug effects in a systematic and timely manner. A proper knowledge regarding severity, causative drugs and health effects generated from active, prospective surveillance has important impact for effective NTEP[2]. Bedaquiline demonstrated excellent minimum inhibitory concentrations (MICs) against both drug-sensitive and MDR-TB. Adverse effects are common with MDR-TB treatment regimens with or without bedaquiline. As Bedaquiline is newer drug there is limited data on its ADRs and efficacy and there are very few studies available on Bedaquiline containing regimen so we like to do this study. We have analysed various ADRs of Bedaquiline and other drugs in bedaquiline containing regimen.

Aims & Objectives

1. To enlist various ADRs in Patient's of DR TB on Bedaquiline regimen.
2. To Assess severity of various ADRs of BDQ regimen.

Methodology

It is a prospective study conducted at the Pulmonary Medicine Department of , AMC MET medical college, LG hospital, Ahmedabad during the period of August 2020 to January 2021, after approval by Institutional Review Board.

ADR is defined as any response to a drug which is noxious and unintended, and which occurs at doses normally used in person for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function[3].During study period, data of patients receiving MDR-TB treatment as BDQ regimen in DR-TB Centre of AMC MET Medical college, for the complaints of ADR is collected regarding age, sex, height, weight, pregnancy, co-morbid illness such as diabetes mellitus, hypertension, dose and duration of MDR-TB drugs, other medications, investigations such as complete blood count, liver function tests (LFT), renal function tests (RFT), etc. are obtained from patients after taking written and informed consent. The patients of DR TB who are on Bedaquiline regimen and who developed any ADRs after starting treatment till the patients are on tablet bedaquiline are taken for study. Patients are accessed for suspected drug causing ADR and analysis is done and patients are re challenged with drugs and in some cases drugs are withdrawn or replaced. All details of ADRs like patient information, suspected ADR, suspected medication causing ADR are recorded in Suspected Adverse drug reaction Reporting Form and data is analyzed.

Data is entered into MS-Exel sheet. Descriptive statistics is used to analyze the data. Results are expressed as either percentage or mean ± standard deviation (SD). Mean ± standard deviation is calculated by using Graph pad prism 5.02.

RESULTS

A total of 100 patients with diagnosed MDR-TB and receiving Bedaquiline regimen therapy are enrolled in the study from August 2020 to January 2021 . Out of 100 patients, 55 (55%) experienced ADR. Rest of data is analyzed with 55 patients who experienced ADRs. Among patients who developed ADRs

it is found that the incidence of ADRs is higher in males (60%) as compared to females (40%) and mean age of patients who developed ADRs is 34.87±10.32 years.(Table-1)

Table 1: Demographic characteristics of MDR-TB patients (n=100).

Characteristics	Value
Total numbers of patients on MDR-TB treatment	100
Gender Male Female	 52 (52%) 48(48%)
Number of patients reporting ADR	55(55%)
Gender (n=55) Male Female	 33 (60%) 22(40%)
Age (years) Mean ± SD Range	 34.87±10.32 15-60

Values are expressed as Mean ± Standard deviation (SD) or number (%); ADR: adverse drug reaction.

Among 55 reported ADRs, Gastrointestinal upset (nausea, vomiting) is the most common ADR reported (42%) followed by Hepatitis(22%),Peripheral neuropathy(11%), QTC prolongation (09%), Hypomagnesemia(5.5%), Redness of skin (5.5%), Optic neuropathy(04%) and Psychosis (02%)(Table-2)

Table 2: Details of ADRs in patients receiving MDR-TB therapy.

Adverse drug reaction	Number of patients with ADR (%)*	Action Taken for ADR
Gastritis	23 (42%)	Symptomatic treatment
Hepatitis	12 (22%)	Symptomatic treatment
Peripheral neuropathy	06 (11%)	Additional Tab Pyridoxine 100 mg/day given
QTC prolongation	05 (09%)	Bedaquiline kept on hold then re started
Hypomagnesemia	03 (5.5%)	Symptomatic treatment
Redness of skin	03 (5.5%)	Symptomatic treatment
Optic neuropathy	02 (04%)	Linezolid replaced by Pyrazinamide
Psychosis	01 (02%)	Cycloserine stopped permanently

ADR: adverse drug reaction. MDR-TB: multi drug resistant-tuberculosis.

Table 2 shows details of ADRs observed in the present study. Gastrointestinal upset namely nausea, vomiting is the most common adverse drug reaction (42%). The causative drugs in regimen are may be PAS, ethionamide, pyrazinamide, ethambutol, bedaquiline, clofazimine, linezolid and fluoroquinolones[4]. In this study PAS is used as a replacement drug in case of drug withdrawal because of GI upset. Out of 23 patients PAS is used as replacement drug in place of Moxifloxacin in 10 patients. Other 13 out of 23 patients are treated symptomatically.

Hepatotoxicity is the 2nd most common adverse drug reaction(22%). Causative drugs in regimen may be bedaquiline, ethionamide and PAS[4]. All these patients are treated symptomatically and none of the patients required drug withdrawal.

Peripheral Neuropathy is one of the major side effect which worsens the quality of life of patients who are on treatment. Causative drugs may be Lzd, Cs, H, Am, FQ, rarely Eto, E . In this study 06 patients (11%) developed peripheral neuropathy so the dose of pyridoxine is increased and dose of Linezolid is decreased after the use of increased dose of pyridoxine symptoms of peripheral neuropathy were decreased and none of the patients required drug withdrawal.

QT prolongation is a common ADR seen in patients treated with bedaquiline. Total 05 (9%) patients developed QT prolongation in this study. The causative drugs may be Bedaquiline, Clofazimine and Moxifloxacin . In this study all three drugs are kept on hold for 10 days in patients who developed QT interval prolongation and serum electrolyte level were done, out of 5 patients 3 patients were having hypomagnesemia, correction was done, after correction ECG was done which was normal and in rest 2 patients electrolytes were normal, 2D echo was done and ECG was repeated weekly and ECG was normal then first tab Bedaquiline then after 1 week tab Moxifloxacin and then after 1 week tab Clofazimine were restarted one by one. ECG turned normal after 2 weeks in other 2 patients.

Redness of skin is seen in 03 patients (5.5%) in this study. Most common drug causing redness of skin is clofazimine. Patients were councelled and skin lotion prescribed for this. Drug withdrawl is not required in any patient.

Optic neuropathy is seen in only 2 patients (04%) in this study. Causative drugs may be Linezolid, Ethambutol, Ethionemide and Clofazimine. As this is a serious side effect Linezolid is replaced by Pyrazinamide in this study. After replacement of Linezolid symptoms decreased in 15 days.

Psychosis is observed in 01 patient (02%) in this study. Causative drugs may be Cycloserine, Isoniazid and fluoroquinolones. Out of all causative drugs main causative agent is cycloserine, so it is stopped permanently. Psychiatric councelling was done and Cycloserine was not re-challanged. Patient did not develop psychosis in followup.

In order to take proper initiatives towards the management of ADRs, it is necessary to study the severity of ADRs. Modified Hartwig and Siegel scale is widely used for this purpose, which categorizes ADRs into mild, moderate and severe[5]. In this study 47% of ADRs are Mild (Level-1), 44% ADRs are Moderate (Level-3 & Level-4) and 09% ADRS are Severe (Level-6)(Table-3). Patients developed severe side effects like optic neuropathy and psychosis which were causing permanent harm to the patients so they required hospitalization and active intervention was done to stop the side effects.(Table-3)

Table 3: Severity assessment of ADRs (n= 50) by modified Hartwig and Siegel scale.

Severity	Level	Number(%)
Mild	Level 1	26 (47%)
	Level 2	00
	Total	26 (47%)
Moderate	Level 3	19 (35%)
	Level 4	05 (09%)
	Total	24 (44%)
Severe	Level 5	00
	Level 6	05 (09%)
	Level 7	00
	Total	05 (09%)

ADR: adverse drug reaction

DISCUSSION:

Drugs used for DR-TB treatment involve a long-term exposure and have greater toxicity effects. A high frequency of adverse drug reactions is one of the major challenges in the treatment of MDR-TB. The present study evaluated various adverse drug reactions in patients receiving treatment for Multi-drug

resistant tuberculosis, and assessed their severity.

The demographic characteristics of patients receiving treatment for MDR-TB (Table 1) in this study are male-60% and female-40%. In previous study conducted by Kapadia et al. male were 63.49% and female were 36.51 which is almost same as present study.[6]

The percentage of Gastrointestinal upset in this study is 42% but the study done by Furin at el and Shin et al all the patients had GI upset.[7].

Hepatotoxicity in this study is (22%) as compared to study done by Molla et al. (8.9%)[8].

In present study Peripheral neuropathy was observed in 11% of patients (Table 2) while in the study done by Shin et al Peripheral neuropathy is seen in 13% which is comparable to present study.[9,10]

QT prolongation is (09%) in this study compared to the study done by Jones et al. which observed 1.2% .This may be because of less patient data in my study.[11]

Optic neuropathy was observed in 04% of patients in this study and it is 5.8% in study done by Mehta et al.[12]

In this study 47% of ADRs are Mild (Level-1), 44% ADRs are Moderate (Level-3 & Level-4) and 09% ADRS are Severe (Level-6) and in the study done by Shinde et al. in which 51.38% of ADRs are Moderate (level 4b) and 35.78% are of Mild category (level-1).[13]

Strength of the study is inclusion of all patients complaining of ADRs to MDR-TB treatment over period of 6 month at single centre where the protocol for management of the patients is same and also present study is prospective. There are some limitations to this study like we have enlisted and analyzed ADRs only for the period of 6 month when patient is on tab bedaquiline so ADRs developed after the period of 6 months is not enlisted so the results of this study could not be generalized to patients receiving MDR-TB therapy in community. Further studies with larger sample size needs to be carried out.

GI upset, QT prolongation and peripheral neuropathy are major concerns in the successful management of MDR-TB with Bedaquiline containing regimen as they commonly lead to drug withdrawal, poor patient compliance and use of less efficient drugs in the regimen. Therefore the patients and their relatives and health workers should be aware of these ADRs for early detection and treatment.

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Conflict of Interest: None
Declaration of Interest: None

REFERENCES

(1). Zero TB deaths: Stop TB in my life. TB India: Revised national TB control programme, annual report. Central TB division, Director General of Health Services. 2013.Available at: http://tbcindia.nic.in/ Write Read Data/ 1892s/ 346740555TB%20India%202013.pdf.
(2). Shinde MP, Halasawadekar NR, Ramanand SJ, Pore SM, Ramanand JB, Patil PT, et al. A study of adverse drug reactions in patients receiving treatment for multi-drug resistant tuberculosis. Int J Basic Clin Pharmacol 2017;6:354- 8.
(3). Edwards, Jeffrey K, Aronson. Adverse drug reactions: definitions, diagnosis, and management. LANCET. 2000;356:1255-9.
(4). Guidelines on Programmatic Management of Drug Resistant TB (PMDT) in India. National TB Elimination Programme. Central TB division, Ministry of Health & Family Welfare, Government Of India, March 2021.
(5). Hartwig SC, Siegel J, Schneider PJ. Preventability and severity assessment in reporting adverse drug reactions. Am J Hosp Pharm. 1992;49:2229-32.
(6). Kapadia VK, Tripathi SB. Analysis of 63 patients of MDR TB on DOTS plus regimen: an LG hospital, TB Unit, Ahmadabad experience. Guj Med J. 2013;68(2):52-7.
(7). Furin JJ, Mitnick CD, Shin SS. Occurrence of serious adverse effects in patients receiving community-based therapy for multidrug-resistant tuberculosis. Int J Tuberc Lung Dis. 2001;5:648-55.
(8). Molla Y, Wubetu M, Dessie B. Anti-Tuberculosis Drug Induced Hepatotoxicity and Associated Factors among Tuberculosis Patients at Selected Hospitals, Ethiopia. Hepat Med. 2021;13:1-8
(9). Shin SS, Hyson AM, Castañeda C, Sánchez E, Alcántara F, Mitnick CD, Fawzi MC, Bayona J, Farmer PE, Kim JY, Furin JJ. Peripheral neuropathy associated with treatment for multidrug-resistant tuberculosis. Int J Tuberc Lung Dis. 2003 Apr;7(4):347-53. PMID: 12729340.
(10). Torun T, Gungor G, Ozmen I. Side effects associated with the treatment of multidrug-resistant tuberculosis. Int J Tuberc Lung Dis. 2005;9:1373-7.
(11). Jones, J., Mudaly, V., Voget, J. et al. Adverse drug reactions in South African patients receiving bedaquiline-containing tuberculosis treatment: an evaluation of spontaneously reported cases. BMC Infect Dis 19, 544 (2019). https://doi.org/10.1186/s12879-019-4197-7
(12). Mehta S, Das M, Laxmeshwar C, Jonckheere S, Thi SS, Isaakidis P (2016) LinezolidAssociatedOptic Neuropathy in Drug-Resistant Tuberculosis Patients in Mumbai, India. PLoS ONE 11(9): e0162138. doi:10.1371/journal. pone.0162138
(13). Shinde MP, Halasawadekar NR, Ramanand SJ, Pore SM, Ramanand JB, Patil PT, et al. A study of adverse drug reactions in patients receiving treatment for multi-drug resistant tuberculosis. Int J Basic Clin Pharmacol 2017;6:354- 8.