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Original Research Article

Study of adverse drug reactions (ADR'S) requiring change in anti-tubercular regimen in multi-drug resistant tuberculosis (MDR-TB) patients in a tertiary healthcare centre

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Abstract

Introduction: Multi Drug Resistant Tuberculosis is fast emerging as a global health problem, especially in developing countries like India with a high Tuberculosis burden and poses a major hurdle in the fight against eliminating Tuberculosis. Considering the long duration of treatment in patients of Multi Drug Resistant Tuberculosis (MDR-TB), it is important to keep an eye on adverse drug reactions (ADR) in these patients during follow up. Severe adverse drug reactions warrant discontinuation of drugs in many patients and can also become a significant factor for poor compliance to second line drugs in Multi Drug Resistant Tuberculosis (MDR-TB) patients.

Materials and Methods: The study was an observational based study conducted in the Department of Pulmonary Medicine of a tertiary healthcare centre in Mumbai between over a period of 1 year. A Total of 60 patients out of 172 patients (34.8%) of MDR-TB having ADR and who required a change in their regimen were identified for the study.

Results: A total of 60 patients of MDR-TB patients were identified who had a change of anti-tubercular regimen due to adverse drug reaction, which were done as per Line Probe Assay (LPA) and Drug Sensitivity Testing (DST) reports of which 38 were females and 22 were males. The most commonly withheld drug was Linezolid in 37 (61.67 %) patients, followed by Cycloserine in 8 patients, Delaminid in 5 patients, Bedaquiline in 4 patients.

Conclusion: Severe ADR's are one of the commonest requiring change in anti-tubercular regimen, leading to poor adherence and suboptimal treatment, especially when drugs like Bedaquilline, Delaminid, Moxifloxacin and Linezolid are to be discontinued.

Keywords: MDR-TB, Adverse drug reactions (ADR's), Linezolid, Bedaquilline, Cycloserine

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1. Introduction

Multi-Drug Resistant Tuberculosis (MDR-TB) has become an emerging global health issue and an obstacle in the fight against ending TB, especially in developing countries and account for significant cause of mortality in TB patients. As per WHO, there were half a million new cases of DR-TB (Drug resistant Tuberculosis) patients of which 78 % of them were MDR-TB patients. An estimated 124 000 (9.1/lakh population) patients were MDR-TB patients in India as per WHO.[1] Treatment of Multi Drug Resistant Tuberculosis is significantly lonfer as compared to Drug sensitive Tuberculosis (DSTB) and is also associated with significant Adverse Drug Reactions (ADR's) .Considering the long duration of treatment in patients of Multi Drug Resistant, it is important that frequent follow ups are ensured for them to look for compliance, clinical improvement and to look for adverse drug reactions (ADR's),[2-4] especially when drugs like and Bedaquiline, Delamanid,[5,6] Linezolid,[7-9] Levofloxacin[10] Moxifloxacin[6,10] have become emerged as important drugs in the regimen of these patients as severe ADR's, if ignored, can lead to poor compliance to the regimen and treatment failure in these patients.

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2. Materials and Methods

The study was an observational based study conducted in the Department of Pulmonary Medicine of a tertiary healthcare centre in Mumbai between over a period of 1 year. A Total of 60 patients out of 172 patients of MDR-TB having ADR and who required a change in their regimen were identified for the study. Drugs were withheld and replaced as per Programmatic Management of Drug Resistant Tuberculosis guidelines issued by Ministry of health and Family welfare, Government of India.[11] Expert opinion from concerned specialities like cardiology, ophthalmology, neurology, otolaryngology and orthopaedics were taken prior to withholding the medications. Patients who gave their consent for the study were included in the study.

3. Results

Out of 173 patients of MDR- TB who visited the department, 60 (34.6%) patients developed ADR warranting change in regimen of which 38(63.33 %) were females and 22(36.66%) were males. The mean age of the patients having ADR's was 35.9 years with the youngest patient in the study being 13 years and the oldest patient in the study being 75 years. The drugs were changed and replaced as per LPA (Line Probe Assay) and DST (Drug Sensitivity Testing) reports in adherence to the PMDT (Programmatic management of Drug Resistant Tuberculosis) guidelines under NTEP (National Tuberculosis Elimination Programme) prescribed by Ministry of Health and Family Welfare, Govt of India in March 2021. The median age of the patients requiring change in the regimen was 30 years.

The most common offending drug was Linezolid involving 37 patients (61.67%) with the most common adverse drug reaction being severe peripheral neuropathy (21 patients) (35%) followed by hematological abnormalities (bicytopenia, pancythopenia) in 11 patients (18.33%) and optic neuritis in 5 patients (8.33%) Cycloserine was withheld in 8 patients (13.33%) due to depression and suicidal idealation. Bedaquiline and Delamanid were withdrawn in 9 patients (15%) due to persistent QTCF prolongation, despite electrolyte correction.

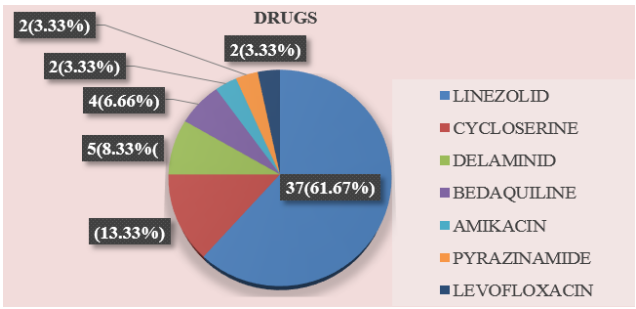

Figure 1: Showing involved the drugs withheld due to ADR

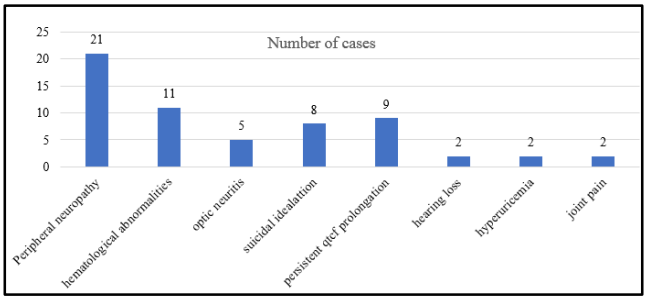

Figure 2: Showing list of ADR's (Adverse drug reactions) requiring drug withdrawal

Amikacin was withdrawn in 2 patients (3.33%) due to severe sensorineural ototoxicity Pyrazinamide was withdrawn in 2 patients (3.33%) due to hyperuricemia Levofloxacin was withdrawn in 2 patients (3.33%) due to joint pain causing severe mobility issues.(**Figure 1**)

4. Discussion

In our study, out of 172 patients, 60 patients (34.8%) of patients in the study required withdrawal of drug due to ADR, which was much higher compared to the study conducted by Mihir Rupani et al, wherein 13.8% of the patients in their study required withdrawal of drug in their regimen due to ADR.[12] Similar percentage (12%) of drug withdrawal from patients' regimen due to ADR were noted in the study conducted by Bhushan et al.[13]

Linezolid was the most common drug withheld in our study involving 37 patients (61.67 percent of ADR cases). Similar rates were found in study conducted by von Lippe et al (70%) although they had a smaller sample size of 7 patients requiring withdrawal of drug from the regimen.[8] Peripheral neuropathy was noted in 21 (35 %) cases and optic neuritis was seen in 5 (8.33%) cases in our study whereas in the study conducted in Shenzen, China; 40 % of MDR TB pts developed neuropathy (optic and/ or peripheral neuropathy); similar to our study.[9] Hematological abnormalities were found in 11 (18.33 %) patients whereas in the study by Pratama et al, it was found in 29 % of cases.[7] (**Figure 2**)

Cycloserine was withheld in 8 patients (13.33%) of the cases. Multiple case reports like the one by Sharma B et al[14] have described cases of Cycloserine induced psychosis but studies involving multiple patients haven't been found regarding psychiatric side effects of cycloserine. More quality research beyond case reports needs to be done regarding adverse effects of cycloserine.

In our study, Bedaquilline or Delaminid were withheld in 9 (15 %) of the patients owing to Qtcf prolongation inspite of treating correctable causes like hypocalcemia, hypokalemia and hypomagnesemia. As per the study conducted by Asfaw T et al, Bedaquiline and/or Delamanid was witheld in 1.4 % of the patients although the latter study had a much larger sample size although they had a much larger sample size of 265 patients.[15]

Amikacin was withheld in 2 patients (3.33%) due to sensorineural hearing loss. In the study by Wrohan I et al, about 28 % patients on injectable drugs for MDR TB experienced sensorineural hearing loss, most commonly noticed in those receiving amikacin and least commonly in those receiving capreomycin.[16]

Levofloxacin was also withheld in 2 patients (3.33%) due to joint pain after orthopedic consultation. Pyrazinamide was also withheld in 2 patients (3.33%). In the study by Mandorva et al, Fluoroquinolones were withheld in 7 % of the cases and Pyrazinamide was withheld in 5 perecent of the cases.[10]

5. Conclusion

Severe ADR's are one of the commonest indications requiring change in regimen, leading to poor adherence and suboptimal treatment, especially when drugs like Bedaquiline, Delamanid, Moxifloxacin and Linezolid are to be discontinued. Since Linezolid was the most common offending drug in the study, extra attention needs to be pain during follow up of these patients and keep a close eye on adverse effects like peripheral neuropathy, hematological abnormalities and optic neuropathy and warn patients regarding signs and symptoms of these ADR's in addition to routine QTCF monitoring of patients who are on Bedaquiline and Delamanid. Also signs of suicidal ideation and psychosis needs to be closely examined in these patients receiving DR-TB regimen. Counselling patients and their care takers regarding these potential adverse effects will ensure their regular follow up and improve their adherence to the anti-tubercular regimen. More studies regarding ADR's should be considered in patients with MDR-TB, especially in high TB burden regions like South Asia and Africa to get an even better understanding of demographics related to these ADR's.

6. Source of Funding

None.

7. Conflict of Interest

None.

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