ORIGINAL ARTICLE

Prevalence of Pre-Extensively Drug-Resistant Tuberculosis (Pre XDR-TB) and Extensively Drug-Resistant Tuberculosis (XDR-TB) among Pulmonary Multidrug Resistant Tuberculosis (MDR-TB) at a Tertiary Care Center in Mumbai

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Abstract:

Background: India is a high burden country for Tuberculosis (TB). As per the World Health Organization (WHO) statistics, 24000 cases of Multi Drug Resistant (MDR) TB were diagnosed in India in 2014. MDR-TB patients consist of a heterogeneous cohort and management has its challenges. *Aims and objectives:* We studied the prevalence of Pre-Extensively Drug Resistant TB (Pre XDR-TB) and Extensively Drug Resistant TB (XDR-TB) among patients of pulmonary MDR-TB not previously exposed to second-line anti-tuberculous drugs and having baseline second-line Drug Susceptibility Testing (DST) against Fluoroquinolones (FQ) and Aminoglycosides (AM). *Results:* We included 227 patients. On the basis of the DST, patients were grouped into- 1) MDR-TB, 2) MDR-TB with FQ resistance {Pre XDR-TB (FQ)}, 3) MDR-TB with AM resistance {Pre XDR-TB (AM)} 4) XDR-TB. Of the 227 patients, 89 (39.2%) had MDR-TB, 127 (55.94%) had Pre XDR-TB (FQ), none had Pre XDR-TB (AM) and 11 (4.86%) had XDR-TB. Nine (4%) patients were human immunodeficiency (HIV) infected and 25(11%) had Diabetes Mellitus (DM). *Conclusion:* This study highlights the importance of baseline DST to FQ and AM in patients of diagnosed or suspected MDR-TB. We encountered a higher prevalence of Pre XDR-TB (FQ) which of concern in management of MDR-TB.

Keywords: Pre XDR-TB, XDR-TB, Baseline Second-Line DST

Introduction:

Tuberculosis is a disease caused by Mycobacterium Tuberculosis (MTB). The disease has a high prevalence in India, accounting for one fourth of the Tuberculosis (TB) cases in the world. India is one of the high burden TB countries in the world [1]. Treatment of tuberculosis involves first and second-line anti-tuberculous drugs for drug susceptible and drug resistant cases respectively. The first-line drugs consist of Isoniazid (H), Rifampicin (R), Pyrazinamide (Z), Ethambutol (E) and Streptomycin (S) which are highly effective with a cure rate of approximately 98% in the new cases. During recent years there has been emergence of resistance to first-line TB drugs. Drug resistance in MTB develops by the selective growth of resistant mutants. Multidrug Resistant Tuberculosis (MDR-TB) is defined when TB bacilli become resistant to both isoniazid and rifampicin or are mono-resistant to rifampicin. Pre-Extensively Drug-Resistant Tuberculosis (Pre XDR-TB) is defined as resistance to rifampicin and/or isoniazid with additional resistance to second-line drugs i.e. to any Fluoroquinolone (FQ), or to at least one of the three injectable second-line drugs {Amikacin, Kanamycin, and Capreomycin (AM)}. Thus Pre XDR-TB consists of two subgroups i.e. 1) MDR-TB with FQ resistance {Pre XDR-TB (FQ)}, 2) MDR-TB with AM resistance {Pre XDR-TB (AM)}. Extensively Drug-Resistant Tuberculosis (XDR-TB) is defined as resistance to rifampicin and/or isoniazid with additional resistance to second-line

drugs i.e. to any FQ, and to at least one of the three injectable second-line drugs (AM). World Health Organisation had estimated about 480000 MDR-TB cases in 2014 out of which only 123000 were detected. About 110000 patients of MDR-TB were put on treatment [2]. Of these around 24000 cases of MDR-TB were diagnosed and initiated on therapy in India [1]. MDR-TB patients form a heterogeneous group with two predominant subgroups, one consisting of those who have not been previously treated with second-line drugs and the other consisting of those who have been previously treated with second-line drugs. World Health Organization (WHO) recommends baseline testing for FQ and AM only among the second-line drugs due to availability of standardised tests and as these two groups of drugs are an important part of MDR-TB treatment regimens across the globe. Data is scarce on the baseline resistance patterns to FQ and AM in the previously not treated group. In our study, we aimed to find the prevalence of Pre XDR-TB and XDR-TB amongst newly diagnosed cases of pulmonary MDR-TB who had never been previously treated with second-line drugs.

Material and Methods:

A prospective study was conducted in a tertiary care hospital and its associated Drug Resistant Tuberculosis (DR-TB) center after ethics committee approval. Mumbai, India adopts criteria C for evaluation of MDR suspects. The preferred choices of tests for rapid diagnosis of MDR-TB are the cartridge based nucleic acid amplification test, Gene Xpert (detects only R resistance) and first-line Line Probe Assay (LPA) (detects H and R resistance) depending on the logistics of Revised National Tuberculosis Control Program (RNTCP). Baseline second-line liquid culture DST has been recently integrated in the RNTCP diagnostic algorithm. Second-line rapid DST like the second-line LPA though available in the city is not included in the diagnostic algorithm citing accreditation reasons though the WHO has accepted it as a rule-in test for XDR-TB. We included 227 adult patients who were diagnosed cases of pulmonary MDR-TB who were never exposed to second-line drugs in their previous anti-tuberculous therapy regimens with available second-line Drug Susceptibility Testing (DST) for Fluoroquinolones (FQ) and Aminoglycosides (AM) reports. Patients unwilling to give consent, previously exposed to second line anti-tuberculous treatment, extra-pulmonary cases and those NOT having baseline second-line DST against FQ and AM were excluded. The DST for AM and FQ was already available at inclusion. It was done by either second-line LPA or liquid culture method (Mycobacterial Growth Indicator Tube method) from a RNTCP accredited laboratory in Mumbai (i.e. Hinduja hospital) either as part of evaluation in the private or public healthcare system from where patients were referred for therapy to us. A detailed history was taken to rule out previous exposure to second-line drugs in the form of anti-tuberculous therapy. On the basis of the available DST, patients were grouped into- 1) MDR-TB, 2) MDR-TB with FQ resistance {Pre XDR-TB (FQ)}, 3) MDR-TB with AM resistance {Pre XDR-TB (AM)}, 4) XDR-TB. Data collected was analyzed statistically in the form of frequency and percentage. The final data was reported as prevalence of XDR-TB, Pre XDR-TB (FQ) and Pre XDR-TB (AM) in cases of pulmonary MDR-TB. Chi-square tests were used to see if there were any age or gender related differences for patients with pre-XDR (FQ) which was the largest group vs. those with only MDR. The patients were treated according to national "Programmatic Management of Drug Resistant TB" (PMDT) guidelines.

Results:

We included 227 patients of pulmonary MDR-TB of which 113(49.8%) were men and 114(50.2%) were women. The second-line DST reports of these patients suggested; 89(39.2%) were MDR-TB sensitive to both the second-line drugs i.e. FQ and AM, 127(55.95%) had Pre XDR-TB (FQ), none had Pre XDR-TB (AM), 11(4.85%) had XDR-TB. Thus the prevalence of Pre XDR-TB and XDR-TB was 55.95% and 4.85% respectively. The 89 MDR-TB patients consisted of 39 men and 50 women. The number of male and female patients with Pre XDR-TB (FQ) was 70 and 57 respectively. The XDR-TB group consisted of 4 men and 7 women. The distribution of patients in MDR-TB, Pre XDR-TB (FQ), Pre XDR-TB (AM) and XDR-TB groups with their sex distribution has been shown in Table 1. The age-wise distribution of patients is given in Table 2. More than 50% of the patients with MDR-TB were in the age group of 18-25 years. The incidence of MDR-TB was inversely proportional to age. A similar trend seen in the Pre XDR-TB (FQ) group. More than 50% of the patients with Pre XDR-TB (FQ) were seen in the age group of 18-25 years which was statistically significant (p=0.02) (Table 3).

Table 1: Patients with MDR-TB, Pre XDR-TB (FQ), Pre XDR-TB (AM) and XDR-TB

Patients	Male	Female	Total	Percentage
MDR-TB	39	50	89	39.2
Pre XDR-TB (FQ)	70	57	127	55.95
Pre XDR-TB (AM)	0	0	0	0
XDR	4	7	11	4.85
Total	113	114	227	100

(Difference in sex distribution is not statistically significant)

Table 2: Age Wise Distribution of All MDR-TB Patients

Age Group	Male	Female	Total	Percentage
18-25	48	72	120	52.84
26-33	20	15	35	15.42
34-41	16	8	24	10.58
42-49	9	11	20	8.82
50-57	14	4	18	7.94
58-65	3	4	7	3.08
66 and Above	3	0	3	1.32
Total	113	114	227	100

Table 3: Age Distribution for patients with Pre XDR-TB (FQ)

Age Group	Male	Female	Total
18-25	34	42	76*
26-33	10	6	16
34-41	10	5	15
42-49	5	2	7
50-57	7	1	8
58-65	1	1	2
66 and Above	3	0	3
Total	70	57	127

*(*Difference in distribution in age group 18-25 is statistically significant, p<0.05)*

The reasons for the same could not be found in this study. Thus we found that overall prevalence of MDR-TB and also the prevalence of Pre XDR-TB (FQ) was higher in the younger age group in the second and third decade in both men and women. The total number of patients in the XDR-TB group was too small to study age-wise distribution trends. No significant gender distribution trends were noted. Of the 227 patients in the study, 9 (3.96%) were Human Immunodeficiency Virus (HIV) infected of which 4 had MDR-TB, 4 had Pre XDR-TB (FQ) and 1 XDR-TB. Of the 227 patients, 25 (11.01%) had Diabetes Mellitus (DM) of which 12 had MDR-TB, 11 had Pre XDR-TB (FQ) and 2 had XDR-TB. The distribution of HIV infected and DM patients is given in Table 4.

Discussion:

We have conducted this study with the intention of knowing the baseline pattern of drug resistance among the pulmonary MDR-TB patients who had not been previously exposed to second line drugs in form of anti-tuberculous therapy. As per WHO recommendations, baseline second-line DST to FQ and AM was studied only. We have found a high prevalence of Pre XDR-TB (FQ) in MDR patients which was 55.95%. In the previous studies from various parts of India, FQ resistance reported ranged from 3% to 35% which had slowly increased from initial surveys of 1996 to recent surveys. The incidence of FQ resistance was found to be 35% in a study done by Agrawal *et al* in 2004 [3] and 24% in a Gujarat survey conducted by Ramachandran *et al* in 2005 [4]. Sharma *et al* had 10% prevalence of FQ resistance in MDR-TB isolates [5]. Study from Zimbabwe between 2007 and 2011 showed the prevalence of FQ resistance to be about 2% [6]. A study done in Delhi by Porwal *et al*, had reported FQ resistance of 7.5% [7]. These were much lower than observed in our study. Dalal *et al* [8] who studied resistance patterns in MDR-TB in Mumbai over 2005 to 2013 reported FQ resistance of 60-65%. Thus our study concurred with higher level of FQ resistance reported in the city however it was significantly higher than the national and international data. The high level of Pre XDR-TB (FQ) is postulated to the widespread use of FQ as antibiotics for most of the common infections

Table 4: HIV Infected and Diabetes Mellitus MDR-TB Patients

Patients	MDR	Pre XDR-TB (FQ)	Pre XDR-TB (AM)	XDR	Total
HIV Infected	4	4	0	1	9
Diabetic	12	11	0	2	25

including pneumonia and pyrexia of unknown origin. When FQ are used as antibiotics they have two detrimental effects, first they have anti-mycobacterial action which can delay the diagnosis of tuberculosis. Secondly, when previously used as antibiotics they can lead to selection of FQ resistant MTB mutants. In some of the case reports and studies [9] it has also been shown that FQ resistance can develop even over a short duration of seven days, which makes the widespread availability and use of FQ in general practice a matter of great concern. Certain unknown demographic factors may also be contributory as the studies from Mumbai have reported higher FQ resistance. We did not find any patient with Pre XDR-TB (AM) in our cohort. Studies by Porwal *et al* [7] and Sharma *et al* [5] reported AM resistance of 5% and 6% respectively in India. Though AM are not used commonly for other infections due to their availability in injectable form, these drugs are also freely available for treatment of most common infections in the community in India. The interesting fact observed was the vast difference in development of resistance to FQ and AM due to unknown reasons. The prevalence of XDR-TB among our MDR-TB patients was 4.85%. The prevalence of XDR-TB among MDR-TB in India in various studies has been reported ranging from 0.89% to 33%. In a study conducted by Rajasekharan *et al*, the prevalence of XDR-TB among MDR-TB was 4.6% [10] similar to our study. Myneedu *et al* reported higher prevalence of 20% XDR-TB among MDR-TB [11]. Sharma *et al* demonstrated a prevalence of XDR-TB to be 2.4% in Delhi, India [5]. In the study of Porwal *et al*, prevalence of XDR TB was about 3.7% [7]. Singh *et al* reported 33.3% XDR-TB in a population of HIV sero-positive MDR TB patients from AIIMS, New Delhi [12]. Mondal *et al* demonstrated 7.4% XDR among MDR strains. A study from Hinduja Hospital, Mumbai revealed 11% of MDR strains as XDR [14]. Thus we did not encounter higher XDR-TB as compared to the national data. Our study was unique as we studied baseline DST to FQ and AM in second-line unexposed MDR-TB patients. Previous studies included a heterogenous cohort of MDR-TB patients and many of them may have been knowingly or unknowingly exposed to second-line drugs.

More than 50% patients in our study were from the age group of 18-25 years. A study done from Nashik, India had 49% patients of MDR-TB in 25-44 years age group followed by 27.5% in 15-24 years [15]. We studied two common comorbidities of HIV and DM among MDR-TB patients. Nine of our study patients were HIV infected which is approximately 4%. This is higher than the reported 2009 NACO [16] adult HIV prevalence of 0.31%, though HIV-TB co-infection data reported from India is variable. Balaji *et al* [17] and Rajasekharan *et al* [10] had reported higher prevalence of 27.9% and 13.9% HIV MDR-TB co-infected patients. In a study conducted in Chennai, HIV seropositivity among MDR-TB was reported as 4.42% [18] consistent with our results. Of the 227 patients, 25 (11%) had DM. This is similar to prevalence of DM in general population as per the national survey data of western India (Mumbai is in western India) [19]. International studies by SP Fisher-Hoch *et al* reported higher DM prevalence of 31.6% in MDR-TB [20]. Fengling Mi *et al* reported the prevalence of DM as 16.6% though there was no significant difference in the prevalence of drug sensitive or drug resistant TB among diabetic patients [21]. Optimal treatment of these conditions is essential with appropriate MDR therapy.

The limitation of our study is that the observed prevalence does not necessarily reflect the prevalence in the community since this was a tertiary care center and in general, referral basis can lead to wide variations in the observed prevalence's amongst different centers. Data from the recent widespread availability of baseline second-line DST to FQ and AM under the aegis of PMDT across Mumbai should further provide the felt need of a large population based study.

Conclusion:

We studied the prevalence of Pre XDR-TB and XDR-TB among MDR-TB patients, which was 55.65% and 4.85% respectively. The high prevalence of Pre XDR-TB (FQ) is alarming and of concern in management of MDR-TB.

Clinical Significance:

With our results we would like to highlight the importance of baseline DST to FQ and AM in all patients of diagnosed or suspected MDR-TB. If these patients are not evaluated with a second-line DST to FQ and AM at the baseline they are bound to get a standardized second-line treatment. In cases of Pre XDR-TB (FQ) and/or AM resistance on prescribing a standardized treatment less number of effective drugs are received by the patient, which can amplify resistance to the effective drugs and cause treatment failure. Availability of the same will lead to prescription of an appropriate modified second-line therapy in MDR-TB wherever required and improve the outcome. The earlier these tests results are available the better and thus the advantages of rapid diagnostics like second-line LPA over liquid culture DST. These are also the recent updated recommendations under PMDT guidelines for India [22] under which MDR-TB patients are treated. These patients should be evaluated for the presence of comorbities like HIV and DM and treated appropriately. We also suggest the importance of reserving FQ and AM for MDR-TB management and curbing their use as antibiotics for all the common infections. Some of the countries and provinces have applied restrictions on the use of these antibiotics in general use with great effect, without having any ill effects on the management of infections and increase in the rates of hospital admissions. If these measures are not applied urgently, the second-line regimen and in particular FQ are bound to fail in the future.

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