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Baseline Fluoroquinolone Resistance among MDR/RR –TB cases: A Retrospective Public Sector Hospital-based Study from Goa, India

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Abstract
The latest guidelines under Programmatic Management of Drug Resistant TB (PMDT) by the National TB Elimination Programme (NTEP) of India provide simplified regimens for various types of DR-TB including shorter oral Bedaquiline-containing regimen for Multi-drug resistant/ Rifampicin resistant TB (MDR/RR-TB) cases. However, baseline resistance to Fluoroquinolones (FQ) renders a patient ineligible for this shorter regimen. A retrospective record-based study was undertaken to determine the proportion of FQ resistance among MDR/RR- TB patients in the public sector in the state of Goa. Data of available baseline Second line- Line Probe Assay (SL-LPA) results of MDR/RR TB patients diagnosed in Goa from January 2018 to December 2021 was analyzed. Of a total of 213 MDR/RR- TB cases, SL-LPA results of 144 cases were available. Of these, 55 (38%), were resistant to FQ (with or without resistance to second-line injectable drugs). 26 (47%) of the FQ-resistant cases were among newly diagnosed MDR/RR -TB cases while 29(53%) were among previously treated TB cases. The high incidence of FQ resistance among MDR/RR -TB cases is a cause for concern and has many negative implications for their management and outcomes.

Keywords: *MDR/RR -TB, SL-LPA, Fluoroquinolone (FQ), NTEP, PMDT.*

Introduction

According to the WHO Global TB Report 2020, India accounts for 27% (1.24 lakh) of the estimated global burden of 4.65 lakh MDR TB cases per year [1].During 2019, 66,255 MDR/ RR-TB cases were diagnosed in India and 56,569 (85%) of them were put on treatment[2]. However, despite many developments and a lot of progress regarding treatment options, the treatment success rate among MDR patients has generally been poor. In India, the success rate of conventional regimens of MDR-TB from 2014 to 2017 was 49%[3]. The introduction of a Shorter MDR-TB regimen with injectable second –line drugs in 2018 showed an improvement of this rate to 60%. Fluoroquinolones (FQ) are a critical component of treatment regimens of drug resistant TB. Guidelines have been set for transitioning to the Shorter oral Bedaquiline –containing MDR/RR TB

regimen by the NTEP in March 2021. However, DST based exclusion criteria makes an MDR/RR-TB patient with baseline FQ resistance ineligible for this new and simpler regimen[3]. Widespread prescription of FQs for trivial infections and their easy availability over the counter has led to increased resistance to these drugs and this poses a major challenge to the clinicians, as it takes away a very potent weapon from the armamentarium against M/XDR-TB treatment[4].

This study aims to estimate the proportion of FQ resistance among MDR/RR TB patients in the public sector in Goa and its implications on management of such cases.

Materials and Methods

This is a retrospective record-based study of the baseline SL-LPA results of MDR/RR-TB cases diagnosed in the public sector under the PMDT programme of NTEP, Goa from January 2018-December 2021. SL –LPA detects susceptibility or resistance to the Fluoroquinolone (FQ) and Second line injectable drugs (SLID) group of drugs. For this study, resistance to FQ; with or without additional resistance to SLID was recorded.

Results

From January 2018 up to December 2021, a total of 213 MDR/RR TB cases were diagnosed in Goa in the public sector. At the time of diagnosis itself, second sample of the patient was subjected to baseline SL-LPA as per the PMDT guidelines.

Out of the 213 MDR/RR TB cases, a total of 144 SL-LPA reports were available. Of these, 49(34%) were resistant to FQ only; while an additional 6(4 %) were resistant to both FQ and SLID. Thus, a total of 55 patients (38%) had resistance to FQ (with or without resistance to SLID) at the time of diagnosis of MDR/RR TB.

Among these 55 cases, the proportion of newly diagnosed i.e., primary MDR/RR TB was 47% (26 cases) while the remainder 53% (29 cases) were previously treated for TB.

Resistance to SLID alone (without FQ resistance) was seen only in 3 cases (2%)

Table No 1: MDR/RR TB patients diagnosed and their SL-LPA results (Jan 2018-Dec 2021)

Total number of MDR /RR-TB cases detected (a)	Out of (a), total no. of SL-LPA reports available (%) (b)	Out of (b)Total no. of MDR/RR-TB cases resistant to only SLID (%)	Out of (b) total no of MDR/RR-TB cases resistant to only FQ(%)	Out of (b) Total no. of MDR/RR-TB cases resistant to FQ and having additional resistance to SLID (%)	Total no of MDR/RR-TB cases having baseline resistance to FQ with/without resistance to SLID (%)
213	144(68%)	3(2 %)	49(34%)	6(4%)	55(38%)

Table No 2: Incidence of FQ resistance in newly diagnosed vs previously treated TB cases

Total no of MDR/RR-TB cases having baseline resistance to FQ with/without resistance to SLID (a)	Out of (a), total no of newly diagnosed MDR/RR-TB (%)	Out of (a), total no of cases who were previously treated for TB (%)
55	26(47%)	29(53%)

Discussion

With more than a quarter of the world's MDR TB burden in India, ensuring good treatment outcomes using well formulated regimens and completing the course within stipulated time frames is of paramount importance. Earlier, patients with rifampicin-resistant or MDR-TB were treated with a combination of second-line drugs, usually for 18 months or more. Recently, WHO recommended a shorter all-oral bedaquiline-containing regimen of 9–11 months duration in eligible patients with confirmed MDR/RR-TB who have not been exposed to treatment with second line TB medicines used in this regimen for more than 1 month, and in whom resistance to fluoroquinolones has been excluded[5]. This simpler and shorter regimen containing Bedaquiline is now available within programmatic settings in NTEP of India and can be given to MDR/RR TB patients who do not have any additional resistance detected; or INH resistance detected with KatG or InhA mutation (not both) & FQ resistance not detected[3].

Worldwide, the proportion of MDR/RR-TB cases with resistance to any fluoroquinolone for which testing was done was 20.1%[1].

According to the 1st National Anti-TB drug Resistance Survey, among MDR-TB patients, additional resistance to any fluoroquinolones was 21.82% (17.33–26.87%), and 3.58% (1.8–6.32%) to any second-line injectable drugs[6].

In India, a study by Selvakumar N et al in Tamil Nadu showed that 18.2% of new and 28.7% of PT patients with MDR-TB had additional OFX resistance[7]. A study by Mamata et al reported an incidence of 32% resistance to FQ among MDR/RR TB isolates tested in a National Reference Laboratory[8]. Similarly, in a study by Prabha Desikan et al, FQ resistance was found in 31.38% of MTB strains having Rifampicin and/or INH resistance in Central India [9].

In our study, a high percentage of FQ resistance (38%) was reported among MDR/RR TB cases in Goa. Among these, 34% were resistant to FQ alone, whereas 4% had additional resistance to SLID drugs also. This high percentage of baseline FQ resistance in a small state like Goa is a cause for concern and deliberation. As a fallout of this, a sizeable proportion of MDR/RR TB cases will be ineligible for the shorter Bedaquiline regimen.

The only option for such patients is the longer regimen in which the success rates have been generally poor. According to the Global TB Report 2020, among 11 210 patients who started treatment for MDR/ RR-TB and were also resistant to fluoroquinolones, and for whom outcomes were reported, 47% completed treatment successfully, 24% died, treatment failed for 11%, and 18% were lost to follow-up or their treatment outcome was not evaluated[1]. The death rates were highest in India.

Another observation in this study is the high occurrence of FQ resistance in newly diagnosed MDR/RR TB cases. In our study, 47% of the FQ resistant cases were newly diagnosed MDR cases. Quinolones being broad spectrum antibacterial agents, their widespread and indiscriminate use, often in subtherapeutic doses, is likely to rapidly enhance quinolone-resistant organisms, including mycobacteria[10]. Studies report that as small as 13 days of exposure to FQs can lead to the development of FQ resistance among treatment naïve and treatment-experienced TB patients. The standard duration of fluoroquinolone treatment is 10-14 days for most bacterial infections. The generation of high-level fluoroquinolone-resistant M. tuberculosis over such a period could severely limit the use of this class of antituberculosis drugs [11]. Besides, use of fluoroquinolones in patients with respiratory infections might delay the diagnosis of active pulmonary TB by nearly 2 weeks[12].This can accelerate the development of FQ resistance in patients. Broadly, it has been noted that the main causes of the increasing spread of resistant TB strains are weak medical systems, amplification of resistance through incorrect treatment, and ongoing transmission in communities and facilities [13].

Conclusion

Our study has noted a high incidence of fluoroquinolone resistance among MDR/RR TB patients (38%) in the public sector, which is a cause for concern since we have limited options for the treatment of pre-XDR/XDR-TB. All efforts should be directed to create awareness among practicing doctors of considering the diagnosis of TB in people with symptoms suggestive of this disease and limiting the use of prolonged or repeated courses of fluoroquinolones in patients generally. The looming threat of Fluoroquinolone resistance mandates discretion in its use, both in drug sensitive TB and other clinical conditions.

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