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Original Research Article

Clinical Profile and Treatment Outcome of H (Isoniazid) Mono Resistant Pulmonary Tuberculosis Patients at Tertiary Health Care Center in South Gujarat

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Abstract

Background: Tuberculosis is a preventable and curable disease. In 2022, TB was the world's second leading cause of death from a single infectious agent. Isoniazid is the first line medicine for the treatment of active tuberculosis and latent TB infection, with high bactericidal activity. Resistance to isoniazid reduces the effectiveness of TB treatment and increases the risk of acquiring resistance to other first line drugs. This leads to increase risk of multidrug resistant TB.

Aim and objectives: The objective is to study clinical profile and treatment outcome in isoniazid mono resistant pulmonary TB under programmatic conditions.

Materials and Methods: This study is a prospective, observational and longitudinal single center study performed at the tertiary health care center in South Gujarat (DRTB NODAL Center). Diagnosed isoniazid (mono- H) resistant pulmonary tuberculosis patients during study period were enrolled and followed up during study to record demographic data, clinical characteristics and treatment outcomes.

Results: In our study, 30 patients of isoniazid mono resistance pulmonary TB were enrolled. The mean age of patients was 36.7 years. Two-third of the patients were male (70%). 63.3% of patients were underweight (BMI < 18.5 kg/m^2). All patients presented with symptoms of cough, fever and anorexia. Primary H mono resistant was detected in 83.3% patients. Most common INH mutation detected on FL-LPA was in the Kat G gene in 60% patients followed by InhA gene in 36.7% patients and one patient had both gene mutation. The most common ADRs observed were gastritis and GIT symptoms (43.3%). In our study favorable outcomes with treatment regimen as per national program guidelines was observed in 28 (93.34%) patients. Unfavorable outcome was observed in form of treatment failure in 1 patient and death in 1 patient.

Conclusion: Most of isoniazid mono resistant TB patients present with primary resistance to isoniazid. Patients who have microbiologically confirmed TB with rifampicin sensitive need to be checked for FL-LPA for isoniazid sensitivity. The availability of rapid diagnostic test and treatment regimen under national program is effective for diagnosis and management of H mono resistant TB.

Keywords: Pulmonary Tuberculosis, Isoniazid Mono Resistant, Adverse Drug Reaction, Treatment Outcome.

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Introduction

Tuberculosis (TB) is a preventable and usually a curable disease. Yet in 2022, TB was the world's second leading cause of death from a single infectious agent. More than 10 million people continue to fall ill with TB every year. TB is caused by the bacillus mycobacterium tuberculosis, which is spread when people who are sick with TB expel bacteria in to the air. About a quarter of the global population is estimated to have been infected with TB. Following infection, the risk of

developing TB disease is highest in the first 2 years (approximately 5%) after which it is much lower. Of the total number of people who develop TB disease each year, about 90% are adults with more cases among men than women. The disease typically affects lungs (pulmonary TB) but can affect other sites as well. Without treatment, the death rate from TB disease is high. With treatments currently recommended by WHO, about 85% of people with TB can be cured. The reported global number of people newly diagnosed with TB was 7.5 million in 2022. Globally in 2022, TB caused an estimated 1.30 million deaths. The net reduction in global number of deaths caused by TB from 2015 to 2022 was 19%. Globally, an estimated 410000 people developed multidrug-resistant or rifampicin resistant TB in 2022. Treatment success rates have improved: to 88% for people treated for drug susceptible TB and 63% for people with MDR/ RR TB. WHO uses five categories to classify cases of drug-resistant TB: isoniazid resistant TB, RR-TB and MDR-TB, extensively drug- resistant TB and pre-XDR TB. Detection of drug resistance requires bacteriological confirmation of TB and testing for drug resistance using rapid molecular diagnostic tests, culture method or sequencing technologies.[1]

Isoniazid is one of the most important first line drug for the treatment of active tuberculosis and latent TB infection, with high bactericidal activity and a good safety profile. The emergence of TB strains resistant to isoniazid threaten to reduce the effectiveness of TB treatment. About 8% of TB patients worldwide are estimated to have rifampicin susceptible, isoniazid- resistant TB (Hr-TB). In patients with confirmed rifampicin susceptible and isoniazid resistant tuberculosis, treatment with rifampicin, ethambutol, pyrazinamide and levofloxacin is recommended.[2]

There are few studies on the clinical profile and treatment outcome of mono H resistance pulmonary tuberculosis. Therefore, this study aimed at observing clinical characteristics and treatment outcome of H mono resistance pulmonary TB.

Materials and Methods

This study is a prospective, observational and longitudinal single center study performed at the tertiary health care center in South Gujarat (DRTB NODAL Center) from June 2022 to August 2024. In this study period, 30 patients were enrolled and follow up was done up to 9 months. All Patients were diagnosed with isoniazid (mono- H) resistant pulmonary tuberculosis cases with age > 18 years, male and female, patients willing to participate in the study. Critically ill patients, any other drug resistance TB (other than mono H) patients, pregnant females were excluded from the study. Isoniazid resistance pulmonary TB patients were started on H mono DR-TB regimen as per the PMDT 2021 guidelines. Above all patient were labelled H mono resistance tuberculosis on the basis of sputum smear AFB positive with Truenat / CBNAAT shows MTB detected with rifampicin sensitive, First Line LPA shows rifampicin sensitive with Inh A and/or Kat G mutation for isoniazid. In all these patients, sputum second line LPA was advised to check resistance of other second line Tuberculosis drugs.

A thorough history, physical and clinical examination and necessary laboratory investigation parameter were analyzed and recorded for these patients at the time of enrollment. After initiation of H mono regimen along with clinical evaluation, patients needs to be closely monitored for bacteriological, radiological improvement on treatment and for adverse events. Sputum sample were tested for smear microscopy for AFB on monthly basis from 3rd month onwards till the end of treatment completed. In patient with extensive disease, if smear at the end of month 4 is found positive the treatment may be directly extended to 9 months. In patients who remain sputum smear positive at the end of 5th month or later treatment outcome will be declared as treatment failed. Sputum specimen for culture was tested at the end of 3rd month, 6th month and/or 9th month (if applicable). At the end of treatment final outcome was noted based on follow up culture results in the form of cured, treatment failed, treatment defaulter and death. [3]

Ethical Consideration: The study was conducted after ethical permission from the institutional ethical committee. The study participants had been explained the nature and purpose of the study and written informed consent was obtained.

Results

In our study, 30 patients of mono H (isoniazid) resistance pulmonary TB were observed and examined. The mean age of patients was 36.7 years. Majority of patients were 18-27 years of age (30%), followed by 28-37 years of age (26.6%), 38-47 years of age (26.6%). Only few patients were observed in age group of 48-57 years (10%) and above 57 years of age (6.6%).

Two thirds of patients (70%, n=21) were male and remaining 30% (n=9) of patients were female, with 2:1 male: female ratio. In this study, majority of patients (63.3%) were underweight (BMI < 18.5 kg/m2), suggest malnutrition were significant concern in those patients and 23.3% patients had normal BMI in range of 18.5 to 24.9 kg/m2, 13.3% patients had BMI >25. In the present study, symptoms of cough, fever, anorexia and weight loss were present in most of the patients. Out of

total patients (n=30), 30 patients presented with symptoms of cough, fever and anorexia, 96.7% patients were presented with symptoms of weight loss, less common presenting symptoms in patients were hemoptysis (30%) and breathlessness (10%).

Out of total 30 cases, 83.3% (n=25) patients were newly diagnosed cases and 16.6% (n=5) patients had previous history of tuberculosis.

In the current study, common findings on chest x ray were cavitary lesion in 60% cases, consolidation in 13% cases, mediastinal or hilar lymphadenopathy in 6.6% of cases, pleural effusion in 3.3% of cases and mixed chest x ray lesions in 16.6% of cases.

The most common INH mutation detected on sputum specimen FL-LPA was in the Kat G gene (n= 18, 60%) followed by Inh A gene (n= 11, 36.7%) while one of our patients had both gene mutation. The sputum specimen with isoniazid mono resistance on FL-LPA were further subjected to SL-LPA, which showed 100% sensitivity to fluroquinolones and second line injectable drugs.

In our study 93.34% (n= 26) patients had sputum smear and culture conversion negative at the end of 3rd, 6th and 9th month of treatment. 3.33% (n=1) patient had sputum smear and culture positive that patient was shifted to All oral longer BDQ based regimen.

In the present study, majority of patients had no adverse drug reactions. Most common ADRs observed were gastritis and GIT symptoms in 43.3% patients followed by hepatitis in 13.3%. Arthritis and arthralgia were observed in 16.7% patients.

In the current study, out of total 30 patients, 93.34% (n=28) patients were cured, 3.33% (n= 1) patient required regimen change and was labelled as treatment failure and 3.33% (n=1) patient died. In our study under programmatic condition, cured was considered favorable outcome while treatment failure and death were considered unfavorable. We observed favorable outcome in 93.34% (n= 28) patients and unfavorable in 6.66% (n=2).

Discussion

In our study, we present data of 30 patients, mean age of patients was 36.7 years. 21 patients (70%) were male and remaining 9 patients (30%) were female. Majority of patients (63.3%) were underweight BMI of <18.5 kg/m2. Most of the patients presented with complaints of cough, fever, anorexia and weight loss. Out of a total 30 patients, 25 patients (83.3%) were newly diagnosed cases and 5 patients (16.6%) had previous history of tuberculosis. Most common INH mutation detected on FL-LPA was in Kat G gene in 18 patients (60%), Inh A gene mutation in 11 patients (36.7%) and in one patient had both gene mutation. Most common ADRs observed were gastritis and GIT symptoms. Out of a total of 30 patients, 93.34% patients were cured.

In our study, mean age of patient was 37 years. In "Karo et al." study median age was 41 year and in "Schechter et al." study median age of patient was 49.6 year. [4,5] This indicating that the disease is common in young to middle aged population.

In our study, two thirds of patients (70%) were male and remaining 30% patients were female. In "Karo et al." study 66.1% patients were male, 33.8% patients were female.[4] In "Lee et al." study 65.7% patients were male.[6] Male: female ratio was comparable with our study.

The majority of our patients (83.4%, n=25) had no previous history of TB. In "Karo et al." study new TB cases 79.4% and in "Lee et al." study 70% patients had no previous history of TB. [4,6]

In our study, out of total 30 cases, chest x ray common findings were cavitary lesion in 60%. In "Lee et al.", study same findings observed in chest radiology in 23.6% patients and in "Schechter et al." study cavitary lesion chest x ray findings were observed in 12 % patients. [5,6]

In our study, we observed that the sputum specimen of our patients predominantly had a mutation in the Kat G gene (n=18, 60%) followed by a mutation in Inh A gene (n=11, 36.7%) and one of our patients had both gene mutation while in "Garg et al." study 75% of patients had Kat G gene and 25% of patients had Inh A gene mutation. [7]

In 2021, Central TB division published guidelines for programmatic management of drug-resistant tuberculosis in India. As per guidelines if Isoniazid resistance is detected in FL-LPA (with Rifampicin sensitive), the patient will be initiated on H mono regimen. All of our patients enrolled in study with Isoniazid resistance were initiated on RZE–Lfx for 6 months, treatment extended directly to 9 months in patients with extensive disease and if smear at the end of month 4 were found positive. The additional resistance to drugs such as Pyrazinamide, Levofloxacin and Linezolid during treatment was replaced with drugs as per PMDT 2021 guidelines.[3]

In our study, out of total 30 cases, 93.34% of cases were cured (favorable outcome) and unfavorable outcome in 6.66% cases. In "Garg et al." study, favorable outcome was in 65.4% patients.[7] In "Karo et al." study successful treatment was observed in 74% cases. [4] In "Schechter et al." study 81% patients were cured. [5] We found that in our study with the use of Rifampicin, Pyrazinamide and Ethambutol with Levofloxacin

led to a high rate of successful outcome among patients with Isoniazid resistant tuberculosis.

Strengths and Limitations: The strength of this study is that, this study was done in a government hospital with National Tuberculosis Elimination Program. Thus, predefined follow up was done optimally and as per schedule with the help of program staff so there was no loss to follow up amongst study participants. The limitation of the study is smaller sample size. This study will not represent the whole Indian population as the study group was comparatively small.

Conclusion

The outcome of Fluroquinolone-based regimen (RZE-Lfx) for patients with isoniazid mono-resistant tuberculosis is favorable, with few non-serious adverse drug reactions. Most patients present with primary isoniazid mono- resistance, with sputum specimen predominantly showing mutation in the Kat G gene. Nutritional support as part of the tuberculosis management protocol is crucial for improving patient outcomes. It is important to rule out drug resistance to isoniazid in patient initiated on standard regimen for DS- TB. The treatment available for isoniazid mono-resistant tuberculosis under the national program is effective and associated with high cure rates.

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