Research Article

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Clinico-Microbiological Profile And Treatment Outcomes Of Patients With Isoniazid Monoresistant Tuberculosis

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1. Abstract

1.1. Background: Isoniazid (INH) is an essential first-line medication for the treatment of tuberculosis.

1.2. Aıms And Objectıves: Tuberculosis drug resistance on treatment outcomes is a topic that is receiving a lot of attention.

1.3. Methods: The study was approved by the Institutional Review Board of Mgmcri (Mgmcri/Res/01/2020/80/IHEC/303 Date:04/03l2021) and performed in accordance with the principles of the Declaration of Helsinki. The study involves a single group of patients who have been diagnosed with Isoniazid monoresistant tuberculosis. Treatment history and demographic data of the patients were obtained after informed consent. Analysis of multiplex PCR and Line Probe Assay (LPA), observed mutation patterns.

1.4. Reuslts: Gene responsible for TB was KATG (67.3%), and it was a prime mutation observed (58.41%). Positive association with males (74%), occupation as coolie (88%), Diabetes as a comorbidity (33%), pulmonary tuberculosis as the TB site (98.01%), history of previous ATT intake in 43 patients, katG mutation (67.3%) . The cure rate was high in INH high-concentration resistance patients, which was statistically significant (p=0.0167). INH monoresistance mutations are seen in 64.3% of the patients with kat G, compared to inh A (34.65%).

1.5. Conclusion: Significant association between males, Diabetes, smoking and alcohol addictions were associated with a high risk of developing high-dose INH monoresistance. Patients who are microbiologically confirmed with pulmonary tuberculosis and Diabetes with rifampicin. Sensitive needs to be checked for LPA for Isoniazid to prevent treatment failure.

Keyword:
INH-resistant, LPA, ATT, katG, inhA

2. Introduction

One of the leading causes of death in developing and underdeveloped countries is tuberculosis (TB) caused by the bacteria Mycobacterium tuberculosis (MTB). According to the statistics provided by the World Health Organization (WHO), there were 6.4 million newly diagnosed cases of Tuberculosis. The incidence of TB is higher in India and claims the lives of over half a million people[1]. Today, India has the highest number of cases of MTR-TB in the world, is responsible for one-fourth of the worldwide disease burden, and has much lower success rates[2]. Tuberculosis is gradually decreasing, and the emergence and spread of Multi-Drug Resistance (MDR) have become a significant obstacle[3]. However, new data indicates that more than half of patients with INH-monoresistant TB may require a treatment course lasting more than six months[4]. Additionally, numerous reports have mentioned significantly varied treatment plans for INH monoresistant TB[5]. Mutations in katG or InhA regulatory genes are significant genes responsible for INH resistance. The principal target of active INH is nicotinamide adenine dinucleotide dependent enoyl-acyl carrier protein reductase, ethionamide (ETH), and prothionamide, which are all encoded by the InhA regulatory region (PTH) [6]. High doses of INH may be effective against M. tuberculosis, with InhA mutations resulting in low-level resistance to the medication [7]. The critical concentrations of INH resistance were categorised as low and high doses with cut-off values <0.2 3g/ml and >1 g/ml, respectively. Low and high concentration INH resistance can be viewed as two separate entities because different genetic changes are assumed to cause each [8] .

Line probe assay (LPA) is a quick method based on polymerase chain reaction (PCR) that is used to identify Mycobacterium

tuberculosis complex as well as drug sensitivity to rifampicin (RPM), Isoniazid (INH) and other first-line drugs. LPA only examines sputum samples that have an AFB smear-positive result [9]. Comparing MDR-TB treatment to non-MDR-TB treatment, unsatisfactory outcomes were more connected with MDR-TB treatment[10]. WHO has established a brief treatment regimen for MDR-TB patients to overcome some of this issues [11]. Studies have been conducted in different nations to identify the factors affecting MDR-TB treatment outcomes in the general population and particular target populations, including adults and children with comorbidities. Investigations have revealed significant regional differences, viz., body Mass Index (BMI) >18.5kg/m2, use of more than four effective medications, and a negative baseline sputum smear; experiencing a surgical resection are some of the variables reported[12]. Other factors viz., use of linezolid or fluoroquinolones, customised treatment, co-infection with HIV, a positive smear at the beginning of therapy, a history of TB treatment, smoking, pre-XDRTB, age>44 years, Ofloxacin resistance, male sex, low body weight at diagnosis, poor treatment adherence, smear positive at the second month of treatment, the use of conventional medicine, and treatment interruptions longer than 14 days [13-17]. Contradictory results have been found for some of the above-mentioned criteria in trials with unsatisfactory treatment outcomes,[18] though furthermore, and there are still gaps in the literature regarding the differences between patients with low- and high-concentration monoresistant TB in terms of baseline traits, therapeutic regimen, side events, and outcomes[7]. The present investigation is proposed to study a) the clinical profile of patients registered for Drug-Resistant (b). Isoniazid drug resistance pattern and the pattern of resistance mutation in these patients by review of Intermediate Reference laboratory (IRL) registry. (c) Treatment outcomes of the INH monoresistant cases as recorded in the DR-TB treatment registry. (d). Correlate the clinical and microbiological profiles with treatment outcomes among patients with Isoniazid monoresistant tuberculosis.

3. Materials and methods

3.1. Study design & population

It is a retrospective record-based study of 101 patients who had been enrolled in the IRL and DRTB registry to have Isoniazid monoresistant pulmonary tuberculosis in the Intermediate Reference laboratory, Puducherry. The study involves a single group of patients who were diagnosed with Isoniazid monoresistant tuberculosis.

3.2. Eligibility criteria

Inclusion criteria: Patients registered in Intermediate reference laboratory and Drug-resistant tuberculosis registry as Isoniazid monoresistant tuberculosis. Patients who have registered to have mutations in the katG gene and inhA gene.

3.3. Exclusion criteria: Patients who had been already diagnosed to have Poly Drug-Resistant Tuberculosis, Multi-Drug Resistant Tuberculosis, and Extensive Drug-Resistant Tuberculosis. Patient records with incomplete information. Sample Size. All Isoniazid monoresistant patients with the above-mentioned inclusion criteria enrolled in the Intermediate reference lab (IRL) from 2014- 2020. The minimum sample size is calculated to be 97 using the below-mentioned formula.

n = (Za)^2[p*q]
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d^2za = 1.96
Estimated proportion (p)=0.5, q=1-p 1-0.5 =0.5
Estimated error (d)=10% (0.1)
Sample size (n) =97

Study Tools. Phenotype and genotype characteristics of patients diagnosed with Isoniazid monoresistant tuberculosis, treatment regimens, treatment failure with the standard regimen and further how many were labelled from Isoniazid monoresistant tuberculosis to poly resistant tuberculosis, multi-drug resistance and extensively drug-resistant tuberculosis.

4. Method of Data Collection

Patients diagnosed with Isoniazid mono-resistant tuberculosis were identified by the collection of data from the Intermediate reference laboratory and drug-resistant tuberculosis registry, Puducherry. Baseline characteristics/parameters to be included are as follows:

- Sex
- age
- Comorbidities
- Smear Positive Status
- Genes associated with the resistance
- Type of resistance – low and high dose Isoniazid resistance.
- history of treatment- new and previously treated. The previously treated case can be relapse (recurrent), failure or default (treatment after default).
- Radiographic Findings – Cavitary lesion, Bilateral lesion, Extensive lesion.

Treatment success and failure in each of the above Characteristics/ Parameters.

5. Data Processing and Statistical Analysis

Data was exported to Medcalc version 19.2.6 for further processing[19]. All categorical variables were expressed as percentages, and the continuous variables were expressed as mean ± standard deviation. The statistical significance of mean differences was compared in two groups using an independent t test, and categorical variables were analysed using the chi square test. All values were considered significant if the p-value was <

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0.05.

6. Ethical Consideration

The study protocol was approved by the Mahatma Gandhi Medical College & Research Institute (Mgmcri) Review board.

7. Results

7.1. Demographic and Clinical Characteristics of Patients

A total of 101 patients diagnosed with Isoniazid mono-resistant tuberculosis were identified by the collection of data from the Intermediate reference laboratory and drug resistance tuberculosis registry, Puducherry, from 2014-2020 was included. The baseline demographics and clinical characteristics of these patients are given in Table.1.

Table 1: Demographic and clinical characteristics of the patients

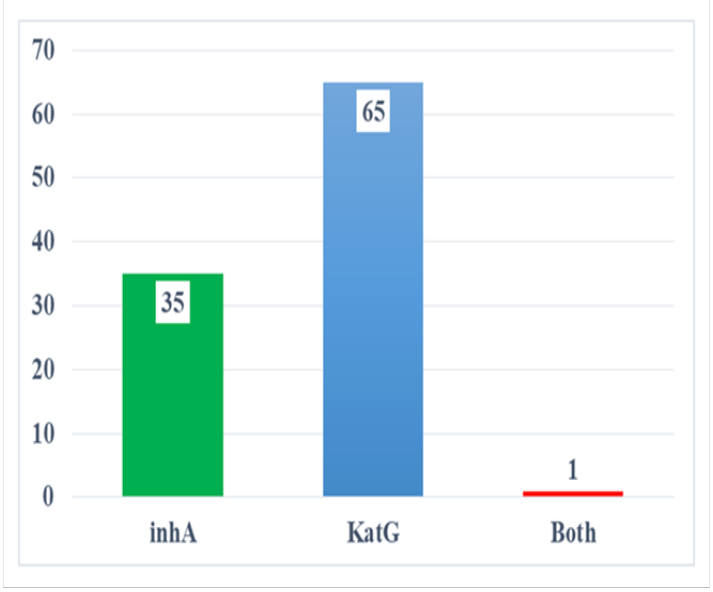
Parameters	*INH low concentration resistance* N=35	*INH high concentration resistance* N=66	p Value
Age	44.54±14.68	44.59±15.80	0.9881
Male	24 (68.6%)	50 (75.75 %)	0.0025
Female	11 (31.4 %)	16 (24.24%)	0.3359
Height in cm	159.20±8.51	159.68±6.53	0.7772
Weight in kg	49.93±12.04	47.92±11.25	0.4142
BMI kg/m^2	18.82±5.42	18.9±4.02	0.9407
H/O ATT	15	28	0.0474
Alcoholism	6	18	0.0484
Smoking	4	10	0.0442
Smoking and alcohol	14	35	0.0213
Pulmonary tuberculosis	30	66	0.0002

Age. Participants mean age was 44.6±15.3 years and ranged from 14 to 87 years, and the predominant age group was between 40 to 50 years . Gender . The predominant gender was male (74%) and followed by female (26%)

7.2. Observed in the study

7.2.1. Height: The average height of the study participants was 159.5±7.22 cm and ranged from 140 to 174 cm Weight . The weight of the study population ranged from 17 to 75 kg with an average of 48.6±11.5 kg. It showed that the majority of the participants were lean body weight Body mass index (BMI). The average BMI was 18.87±4.51 kg/m2, which showed a normal range. However, around 28 % of patients who had below-normal BMI were observed . Blood glucose. Blood glucose levels (supplementary figure) were determined, and it found that the fasting blood glucose levels were higher (177.93±82.50 mg/dl) than random blood glucose levels (159.27±90.04 mg/dl)

Figure 1: Pattern of gene mutations



7.2.2. Marital status: The majority of the study population was married (93%), followed by 4% and 3 % of patients who were single and unmarried, respectively

7.2.3. Occupation: The study population belongs to coolie (88%) followed by students (6%), house-wife (4%), and doctors and salesmen 1% each

7.2.4. Addictions: Smoking was found to be associated in 45% of the patients. Alcoholism was found in 50 % of patients. No addictions were found in 15% of patients.

7.2.5. Comorbidities: Diabetes mellitus (DM) was the only comorbidity observed, which was 33.67%, systemic hypertension at 20.97%, coronary artery disease at 6%, and 4% of the study population did not have any comorbidities

7.2.6. TB Site: Study population, the majority of the patients had pulmonary tuberculosis (98.01%), and 1.98% of the population had extrapulmonary tuberculosis

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8. Clinical Characteristics of the study population

8.1. History of anti-tuberculosis treatment: A history of previous ATT was observed in 43 patients (42.6%). Among 43 patients, sputum was positive at diagnosis and retreatment was found in 31 patients (72.1%). Besides, 58 patients (57.4%) did not have any previous history of ATT.

8.2. Gene is responsible: The gene responsible for INH monoresistant TB were KAT G (67.3%) and INH A (32.7%) of patients

8.3. Mutation Pattern: The katG Mut1 was a prime mutation observed in the present study population (58.41%). Besides, inhA Mut1 was found in 23.76%, inhA Mut1 present &WT1absent in 7.9%, katG Mut1 present & WT1 absent in 6.9%, and other mutations were observed in 2.97%. Comparison of clinical-microbiological profile in INH low and high concentration resistance. The mean age of the patients with low- and high-concentration mono-resistant TB were 44.54±14.68 and 44.59±15.80 years but statistically not significant (P=0.9881) The male gender was significantly higher (75.75%) in high-concentration mono-resistant TB (p=0.0025). Besides, the female gender was not significantly differed between the two groups of patients (p=0.3359). The average height of low and high-concentration mono-resistant TB was 159.20±8.51and 159.68±6.53 respectively and was not statistically significant (p= 0.7772)

The mean weight of low and high-concentration mono-resistant TB did not show any statistically significant difference (p=0.4142). The mean body mass index (BMI) in low-concentration mono-resistant TB was 18.82±5.42, and in high-concentration mono-resistant, TB was 18.9±4.02, which was statistically no significant difference (p=0.9407). The previous history of ATT was higher in high-concentration resistance than in low-concentration, which was statistically significant (p=0.0474). Smoking and alcoholism as an addiction history were predominant and significantly higher in high concentrations than in low concentrations (p=0.0373). TB in the pulmonary region was predominant and significantly higher in high concentrations than in low concentrations (p=0.0002) .

9. The pattern of Gene mutation

The most common mutation in INH-resistant strains was in the katG gene (64.35%), followed by the inhA gene (34.65%). In 1 (1%) patient, both inhA and katG gene mutations were observed (Figure 1). Comparing the pattern of gene mutations in INH monoresistant strains revealed that of 35 isolates with only inhA gene mutation, WT1 pattern was absent and MUT1 present in 8 (22.9%) strains, WT2 pattern was absent and MUT1 present in 3 (8.6%), while MUT1 pattern was present in 24 (68.6 %) strains. KatG gene mutation patterns were observed in 66 isolates with different sequences. WT1 was absent, and MUT1 was present in 6 (9.1%), inhAWT2 was absent, and inhA MUT1 was present in 1 (1.5 %), MUT1 was seen in 58 (87.9%) patients.

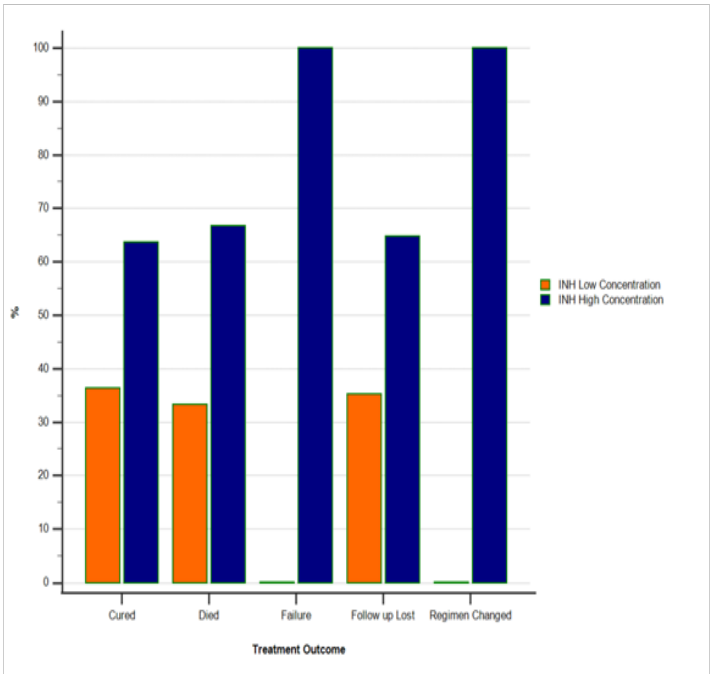
9.1. Treatment impact on weight

Treatment impact on patients' weight was determined, and it was found that weight gain was a major outcome in both low and high concentrations. However, the weight gain and weight loss were not statistically significant (p=0.0622) (p=0.7247) .

9.2. Treatment outcome

Out of 101 INH monoresistant tuberculosis patients, 35 had low-dose concentration resistance (inhA), of which 28 patients were cured. 66 patients had high dose resistance (katG), of which 49 patients were cured (Figure 2). The cure rate was high in INH high-concentration resistance patients, which was statistically significant (p=0.0167).

Figure 2: Treatment outcome between two groups



10. Discussion

Isoniazid helps to prevent the selection and formation of a drug-resistant TB population when used in combination with other anti-TB medications. According to recent studies,20-21 individuals with Isoniazid mono-resistant TB fared worse than those with drug-susceptible TB, despite studies from the 1970s and 1980s reporting a low rate of treatment failure for those receiving four or five medications over a six-month period. Recently, India and Indonesia, Peru, South Africa and Romania found that of 43%, 12.5% of TB patients had Diabetes, respectively22-23. The WHO strategy of routine bidirectional symptom-based TB screening

in known DM patients in high TB burden countries has been endorsed by Alisjahbana et al.24. Current study Diabetes patients having 54% history of previous tuberculosis and ATT intake are having high dose isoniazid monoresistance (katG). The people who had arrived for the presumed TB test were overwhelmingly male and made up 74% of those with MTB positivity. Results are in line with those of recent studies in India that found that 70% of TB patients were males, as reported 25. More than one gene or gene complex, including the katG, inhA, and kasA genes, as well as the intergenic region of the oxyR ahpC complex, may be altered in the genetic foundation of INH resistance26. Studies have demonstrated a correlation between high and low levels of INH resistance and the codon 315 of the katG gene (50%–90%) and the regulatory region of the inhA gene (20%– 35%)27. The present study found that the katG gene (67% of patients had this mutation) was followed by the inhA gene (33% of patients).

Niehaus et al. (2015) discovered that 33.1% of 924 isolates, or 30.3% of those with MDR TB, 47.2% of those with pre-XDR-TB, and 82.8% of those with XDR-TB, carried an inhA mutation with or without a katG mutation28. Clinicians should be aware of mutations in the katG or inhA promoter region. and a high level of resistance to INH is indicated by the existence of mutations in katG alone or in conjunction with inhA29. On the other hand, a mutation restricted to inhA is typically associated with a low level of INH resistance, and these people are likely to benefit from large doses of INH (10–15 mg/kg/day)30. Treatment outcomes showed 77 patients were cured (74.75%), 17 patients were lost to follow-up (16.5%), three patients died during the course of treatment (2.91%), treatment failure was seen in 2 patients (1.94%), treatment regimen changed in 1 patient (0.97%). The study showed a positive association with males (74%), occupation as coolie (88%), Diabetes as comorbidity (33%), pulmonary tuberculosis as the TB site (98.01%), history of previous ATT intake in 43 patients (42.6%), katG mutation (67.3%), katG Mut 1 was the prime mutation (58.4%). The study also showed that male patients with Diabetes have comorbidity, with a history of ATT intake along with sputum positive at diagnosis and retreatment (72.1%) were associated with INH high dose monoresistance (katG), having katG Mut 1 as prime mutation.

11. Conclusion

Due to effective screening implementation of the NTEP program and there has been a rise in the incidence of INH monoresistance tuberculosis in the past few years, raising concern for the increase in the risk of treatment failure and multi-drug resistant tuberculosis. There is a significant association between males, Diabetes, smoking and alcohol addictions associated with a high risk of developing high-dose INH monoresistance (katG). Study concluded that the high prevalence of habits and prevailing low socioeconomic class influenced treatment outcomes, the incidence of recurrent cases and the increased risk of developing INH monoresistance tuberculosis. Patients who are microbiologically confirmed with pulmonary tuberculosis and Diabetes with rifampicin-sensitive status needs to be checked for LPA for isoniazid sensitivity status to prevent treatment failure.

12. Acknowledgements

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