ASSESSMENT OF ADVERSE DRUG REACTIONS AND RISK FACTORS ASSOCIATED WITH FIRST-LINE ANTI-TUBERCULOSIS THERAPY

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ABSTRACT: *The purpose was to investigate and monitor the occurrence of adverse drug reactions (ADRs) from anti-tuberculosis medications in tuberculosis patients. It was a questionnaire-based cross-sectional study. The investigation was performed in different tertiary hospitals starting from March 2024 to June 2024. The investigation was conducted to understand the outcome and relative ADR of first-line anti-tuberculosis treatment. The findings showed that 80% of patients experienced skin rashes, and 50% developed optic neuritis or peripheral neuropathy. The main ADRs included nerve damage in limbs, dizziness, liver toxicity, skin rashes, loss of appetite, diarrhoea, fatigue, jaundice, joint pain, gout, and inflammation of the optic nerve. Specifically, 50% experienced peripheral neuropathy, 40% dizziness, 63% liver toxicity, 34% jaundice, 78% skin rash, 50% optic neuritis, 36% joint pain, and 22% malaise, and 22% gout, with only 3% reporting anorexia. This study showed a high incidence of ADRs with anti-tuberculosis drugs, particularly neuropathy and liver toxicity from isoniazid, optic neuritis from ethambutol, and rash or liver issues from rifampicin. These ADRs, along with potential patient non-compliance, underscore the need for patient education, close monitoring, and tailored interventions to help prevent multi-drug-resistant tuberculosis.*

Keywords: ADR, Ethambutol, Isoniazid, Pyrazinamide, Tuberculosis

1. INTRODUCTION

Tuberculosis is a contagious disease primarily affecting the respiratory system, caused by the *Mycobacterium tuberculosis* (TB) bacterium. However, it can also impact other parts of the body, including the abdomen, bones, joints, lymph nodes, and even the nervous system [1]. Tuberculosis spreads through airborne transmission when tiny droplets containing the bacteria are released into the air during activities like speaking, coughing, or sneezing. These moisture-laden particles allow the bacteria to disperse and easily infect others, making tuberculosis a highly contagious disease [2].

The bacterium responsible for tuberculosis is surrounded by a mycolic acid layer and coated with arabinogalactan, which increases its lethality and resistance, respectively. Its multiple lipid layers enable it to survive within macrophages, promoting the progression of chronic infections [3]. The bacteria are a non-motile, rod-shaped organism that preferentially grows in well-oxygenated areas of the body, such as the upper parts of the lungs, making these regions primary targets for TB infection. The bacterium's slow duplication rate, with a generation time of 15 to 20 hours, increases its ability to cause disease by reducing its detection and attack by the immune system, allowing it to establish a chronic infection [3].

From an epidemiological perspective, TB remains one of the deadliest communicable diseases globally. The infection has remained a significant burden on health despite progress in diagnosis and treatment, and remains rampant, especially in third-world countries. In 2020, approximately 10.4 million people developed TB, and 1.8 million of them died, with more than 95% of reports in low and middle-income countries [4]. For instance, India reports approximately one-fifth of the global TB burden; TB incidence is estimated at two million cases yearly making India the country with a high burden of TB [5]. Pakistan ranks sixth worldwide in tuberculosis incidence, with around 300,000 new cases reported each year [6].

The treatment of TB typically involves a combination of several antibiotics administered for a minimum of six to nine months. The regimen usually includes isoniazid, rifampicin, ethambutol, and pyrazinamide [7]. Drug resistance in TB indicates that treatment with standard medications is ineffective, necessitating the use of more complex antibiotics. This study examines the ADRs associated with first-line therapy in patients with multi-drug-resistant tuberculosis (MDR-TB).

Multidrug-resistant tuberculosis (MDR-TB) poses a serious global health threat, involving strains of Mycobacterium tuberculosis that resist isoniazid and rifampicin, the most potent first-line TB drug [8]. MDR-TB occurs from inadequate TB control, early discontinuation of treatment, and poor-quality drugs. About 410,000 new and previously treated cases of MDR-TB or RR-TB were identified globally in 2022, which are 3·9% and 21% of respective global numbers [9]. The management of MDR-TB is difficult with patients requiring second-line drugs for 18-24 months though shorter duration regimens exist in some clients. MDR-TB increases mortality risks, burdens healthcare systems and endangers global TB control therefore addressing this concern, improves healthcare systems and accessibility to care.

2. METHODOLOGY

Study Design and Setting

A cross-sectional multicenter study was conducted across several tertiary care hospitals in Lahore, including Pakistan Gulab Devi Chest Hospital, General Hospital Lahore, Jinnah

Hospital Lahore, and Mayo Hospital Lahore. These facilities were selected due to their capacity to provide tuberculosis treatment to a substantial population in the Punjab region.

Data Collection

Data were collected using a questionnaire designed to gather information on all known ADRs associated with first line anti-TB medications. The questionnaire included questions about sputum test results, medications used, confirmation of anti-TB treatment, medication compliance, drug side effects. Participants were recruited from male and female patient wards, and informed consent was obtained after providing a clear explanation of the study objectives. Consent for data collection was sought in advance, and the questionnaire was crafted in plain language to facilitate ease of completion for the patients.

Variables

Data were collected prospectively on the following variables:

- Socio-demographic data: age, sex, employment status, housing status, medical information, smoking history, alcohol or drug use.
- Clinical history: Information was collected regarding their tuberculosis history, the onset of symptoms, and whether they have other conditions such as HIV.
- Diagnostic methods: Both sputum smear results and culture sensitivity were recorded, along with the dates on which these diagnostic tests were conducted.
- Treatment details: Details were gathered on prescribed medications, dosages, symptoms, the start and end dates of the treatment plan, level of improvement, and patient compliance.
- Treatment outcomes: cure, treatment success, treatment failure, death, transfer out, loss to follow up or abandonment due to all causes including TB.

Sampling Method

The sampling technique employed was purposeful sampling, focusing on eligible patients from the target population. Consent for data collection was obtained from the hospital management. The participants included were active TB patients who had received Directly Observed Therapy (DOT) instructions and had completed two or more doses. Additionally, patients needed to have been treated with the medication for at least two months without interruption, be aged between 30 and 65 years and could be either male or female. The study excluded patients with latent tuberculosis, those with tuberculosis at other sites, and individuals undergoing treatment for less than two months.

Data Analysis

Statistics were applied to determine incidence of ADRs associated with first line anti-TB drugs using SPSS Statistics software (IBM, version 29).

3. RESULTS

Study Overview

The purpose of this work was to determine the ADRs caused by anti-TB drugs and also to evaluate the risk factors of TB in Pakistan.

Demographics

The total number of participants was 200, of which 54 % were male (n=110) and the remaining were female (n=90). Out of the sample, the largest proportion (98.3%) was from Punjab, while the rest (1.7%) hailed from Khyber Pakhtunkhwa, Pakistan. Participants were categorized into four age groups: 25% of respondents were between 20 and 30 years old, 7.5% were between 30 and 40, 12.5% were between 40 and 50, and the majority, 75%, were between 50 and 60 years old. Of the respondents, 45.3% lived in rural areas, while 54.7% resided in urban areas.

Medical History

Among the participants, 92% had never previously received TB treatment, while 7.7% had a history of past TB treatment. A higher proportion of respondents, 16%, were found to be HIV positive. The majority, 89.3%, had additional health conditions, while only 10.7% had no comorbidities.

Medication Usage

Self-medication was reported by 15% of participants, while 93% sought advice from a pharmacist or physician. Additionally, 12.5% of respondents reported using homoeopathic treatments.

Symptoms of Tuberculosis

The symptoms observed among 196 patients included fever, weight loss, and a productive cough with sputum. Additional symptoms reported were night sweats (28.6%), chest pain (17.1%), reduced appetite (13.0%), and weakness (6.1%).

Diagnostic Methods

Chest X-rays were performed on 60% of patients, sputum smear microscopy on 53%, and polymerase chain reaction (PCR) or GeneXpert tests on 58%. Traditionally, TB diagnosis has relied heavily on a combination of sputum tests, blood tests, chest X-rays, and patient history.

ADR Involving the First Line Anti-TB Drugs

The analysis of ADRs revealed several challenges impacting patient care and treatment adherence. The results are outlined below (Figure 1).

Isoniazid

Peripheral neuropathy was the most frequently observed ADR in patients treated with isoniazid, affecting 60% of patients, particularly those who were immunocompromised. Additionally, hepatotoxicity was noted in 64% of patients, highlighting the importance of regular liver function monitoring.

Rifampicin

Hypersensitivity reactions were the most frequently reported ADR, affecting 78% of patients, with rash as the most common symptom. Anorexia was reported by 12% of patients, highlighting the drug's impact on nutritional status. Additionally, rifampicin caused red-colored urine, which contributed to non-compliance, particularly in older patients with pre-existing liver conditions.

Pyrazinamide

The use of pyrazinamide has been observed to cause hepatotoxic reactions though jaundice was seen in 34% of the patients. This dispels the possibility of distant liver function monitoring scarcely during the treatment period. The musculoskeletal side effect most commonly observed in patients was arthralgia and was severe enough to necessitate NSAIDs in 36% of patients. This is supported by the fact that 22% of patients experienced malaise, which negatively affected their overall health status.

Ethambutol

Ethambutol was associated to both the ocular and metabolic side effects. Optic neuritis was revealed to be the most frequent ADR being reported in 50% of the patients, especially adults. This condition is characterized by eventual dose adjustment and interaction with ophthalmologists to avoid long-term irreversible vision loss.

4. DISCUSSION AND CONCLUSIONS

The findings indicated that ADRs significantly impacted patients undergoing anti-TB treatment, particularly with first-line medications. Notable potential ADRs included hepatotoxicity, neuropathy, and gastrointestinal intolerance. Hepatotoxicity, consistent with findings from previous studies, was also observed in the patients [10-11]. Earlier investigations, along with various regional and international studies, identified isoniazid and rifampicin as the main contributors to liver toxicity, primarily due to their hepatic metabolism. These medications have been consistently linked to adverse effects on liver function, emphasizing the need for careful monitoring in patients undergoing treatment. Nevertheless, a study carried out in a specific South Asian population reported a reduced incidence of drug-induced hepatotoxicity. The researchers proposed that

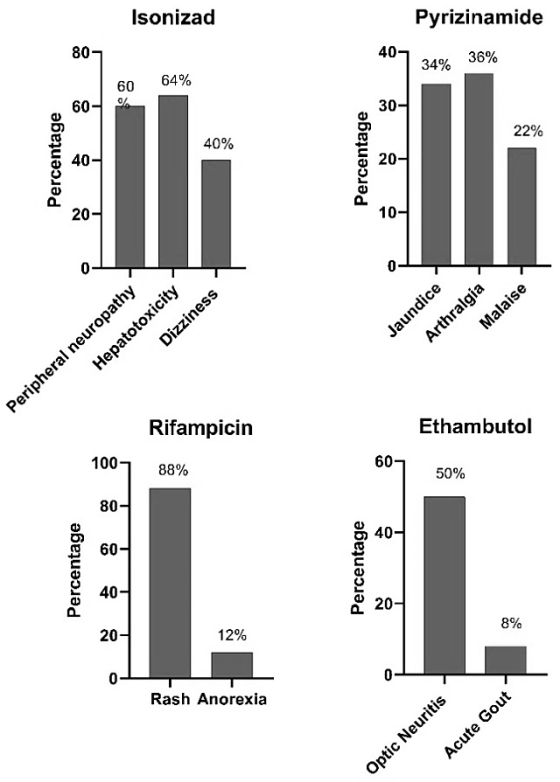

Figure 1. ADRs associated with first-line anti-TB drugs.

factors such as genetic predisposition and nutritional status may play a role in determining sensitivity to these adverse effects [12]. These findings indicate that while ADRs are a global issue, their variety and severity can vary significantly based on regional, patient, and systemic factors. Additionally, the prevalence of ADRs was found lesser in populations that implement effective monitoring and management strategies. For instance, in countries where tuberculosis has been effectively controlled, the incidences of severe ADRs were significantly reduced. This improvement can be attributed to diligent patient follow-up and the implementation of effective management measures aimed at minimizing adverse effects [13]. This discrepancy highlights the need to establish a robust pharmacovigilance system in countries like Pakistan to reduce the potential risks associated with anti-TB medications.

A significant factor contributing to the development of MDR-TB is poor adherence to treatment protocols and the inappropriate use of antibiotics. Notably, we identified that 42.3% of participants have used incorrect antibiotics. It could be a critical factor in the emergence of multidrug-resistant tuberculosis. These findings align with existing literature, particularly from the Europe and Central Asia region, where improper drug usage and insufficient treatment regimens have contributed to an increase in MDR-TB cases [14]. In contrast, studies from high-income countries like the USA present a different scenario, as the incidence of MDR-TB is significantly lower due to stringent treatment protocols and superior healthcare facilities [15]. It is already established that the lack of structured treatment regimens for tuberculosis and the limited availability of second-line drugs in Pakistan pose significant challenges in controlling MDR-TB [16]. This situation necessitates a more rigorous focus on ensuring patient adherence to treatment and the appropriate use of antibiotics.

Our study's findings align with global trends in MDR-TB prevalence, especially in lower-middle-income countries, where inadequate tuberculosis management continues to be a significant concern [17]. In comparison to other South Asian countries, Pakistan's burden of MDR-TB is similar to that of India and Bangladesh, where high population density and under-resourced healthcare systems present unique challenges for transmission and treatment outcomes [18]. In contrast, data from Sri Lanka show a significantly lower incidence of MDR-TB, likely due to more effective national control measures and improved healthcare initiatives for tuberculosis [19]. These regional differences highlight the need for developing country-specific strategies to combat the spread of MDR-TB in healthcare facilities within each nation. While the incidence of MDR-TB in Pakistan is generally comparable to that of other developing nations [20-21], it remains significantly higher than in well-developed countries. This disparity underscores the challenges faced by countries like Pakistan, where resource limitations and healthcare infrastructure affect disease management and treatment outcomes. In contrast, developed countries, with their robust healthcare frameworks and comprehensive public health strategies, are better equipped to control the spread of MDR-TB, resulting in markedly lower incidence rates [22]. In this context, Japan and Germany exhibit markedly lower prevalence rates of MDR-TB, thanks to their effective tuberculosis monitoring systems and strict adherence to DOT guidelines [23-24]. The implications of these findings are evident: it is imperative to enhance tuberculosis treatment regimens in Pakistan, particularly in addressing ADR strains, to prevent the emergence of MDR-TB. To achieve this, it is

essential to implement pharmacovigilance systems, prioritize patient education on adherence to treatment, and develop policies aimed at reducing self-medication practices. An additional advantage is that enhancing the ability to identify and manage ADRs could reduce patient non-adherence, ultimately resulting in lower levels of MDR-TB.

Analysis of global practices shows that countries employing an integrated approach to tuberculosis control, including DOT, achieve significantly higher treatment success rates and exhibit lower levels of drug resistance [25]. Implementing such approaches in Pakistan has the potential to streamline treatment processes while also managing the impacts of ADRs and controlling the spread of MDR-TB. Moreover, by providing targeted training for healthcare professionals on the early screening of ADRs and MDR-TB risk factors can enhance preventive healthcare efforts, ultimately reducing the tuberculosis disease burden within communities.

5. ACKNOWLEDGMENT

The authors would like to express their sincere gratitude to the Medical Superintendents and administrative staff of Mayo Hospital Lahore, Gulab Devi Chest Hospital, General Hospital Lahore, and Jinnah Hospital Lahore for their valuable support and for facilitating access to patient records and data essential for this research. This study would not have been possible without their cooperation and dedication to advancing medical knowledge.

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