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RESEARCH ARTICLE

EXTENT OF HEPATOTOXICITY OF ANTI-TUBERCULOSIS DRUGS USED IN PAKISTAN: A CROSS-SECTIONAL STUDY

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Abstract

Introduction: Tuberculosis is an infectious disease with high rates of infection and mortality throughout the world, but its spread is greater in developing countries, and its control is difficult. It is known that the most common side reaction of drug treatment for tuberculosis is hepatotoxicity resulting from the drugs, which negatively affects adherence to treatment as a result of patients not continuing to use it.
Objective: This study aimed to determine the extent of hepatotoxicity as a result of drug treatment for tuberculosis.
Methods: The study is a cross-sectional study conducted on TB patients undergoing TB treatment in a general hospital in Islamabad, Pakistan. A data collection form was used to obtain demographic and treatment data. The hepatotoxicity of TB drug therapy was evaluated by performing liver function tests (LFTs).Study duration was of 4 months.
Results: The study showed that out of 100 tuberculosis patients, 55 patients were hepatotoxic. Hepatotoxic population includes 26% males and 29% females including almost 10% children either male or female. The maximun hepatotoxicity was observed in the patients undergoing combination therapy. Around 3-5 % patients showed that the Serum-GlutamicPyruvic-Transaminase (SGPT) values more than 2 times of their normal values. While other 50% showed hepatotoxicity 1-2 times of their normal values. Most of the patients found were in the age group ranging from 35-60 years. The main drugs used in tuberculosis treatment were: Isoniazid, Rifampicin, Pyrazinamide, Ethambutal.
Conclusion: The rate of hepatotoxicity in TB patients on anti-TB treatment was high. The current study concluded that the more we move towards a greater number of drugs in combination, the greater the extent and chance of hepatotoxicity. The combination of three anti-tuberculosis drugs (isoniazid, rifampicin, and pyrazinamide) resulted in maximum hepatotoxicity.
Keywords: Ethambutal, hepatotoxicity, isoniazid, pyrazinamide, rifampicin, SGPT, tuberculosis.

INTRODUCTION

Tuberculosis is arespiratory infectious disease that is arised by the bacteria "*Mycobacterium tuberculosis*"[1]. Tuberculosis is characterized by the presence of casemate necrosis, destruction of parenchymal lungs, and the creation of cavities[2]. There exists a hypothesis suggesting that the deterioration of lung tissue caused by tuberculosis is influenced, to some extent, through the deposition of metalloproteinase that are produced through mononuclear phagocytes[2].

Globally, the incidence of tuberculosis in 2020 was approximately 20 million cases, with a modest annual decline of only 1-2%[3]. Furthermore, it is often believed that a staggering number of approximately 2 billion individuals have encountered the tuberculosis bacillus, consequently placing them at potential jeopardy of developing an active manifestation of the ailment[1]. The issue is exacerbated by a significant rise in prevalence

of multidrug-resistant *M. tuberculosis*[4]. The prevalence of tuberculosis in Pakistan is 0.23% according to WHO statistics[3].

Mycobacteria that evade immune responses can disseminate through the circulatory and lymphatic systems, reaching many organs, particularly those that are highly oxygenated such as the lungs, kidneys and bones[5]. Pulmonary tuberculosis is the most prevalent kind of TB (tuberculosis) and skeletal tuberculosis accounts for approximately 33% of tuberculosis cases that manifest in places outside of the lungs[4].

The present treatment for tuberculosis (TB) involves a combination of four medications, namely rifampin (RIF), isoniazid (INH), pyrazinamide (PZA) along with either ethambutol (EMB) or streptomycin (STR)[6]. The administration of these four medications spans a duration of 2 months, which is referred to as the intensive phase[7]. This is then resulted by RIF along with INH administration for a period of 4-7 month, known as continuation phase[5]. Consequently, the entire duration of treatment ranges from 6-9 months[8]. Due to the challenges associated with eliminating Mycobacterium tuberculosis from tissues using existing medications and the prolonged duration of tuberculosis treatment, a significant number of patients exhibit non-adherence to their drug regimen or prematurely discontinue therapy[9]. This lack of adherence has resulted in the prevalence of drug resistant strains of M. tuberculosis[6]. Multidrug-resistant tuberculosis (MDR-TB) is characterized by the presence of Mycobacterium tuberculosis isolates that exhibit resistance to both rifampicin (RIF) and isoniazid (INH)[10]. To establish a cure, a treatment regimen consisting of a combination of second-line medications, which are comparatively less effective and more toxic, may need to be administered for duration of up to 24 months[11].

Patients who exhibit resistance to these initial medications are administered second-line treatments[5]. The medications "ofloxacin and ciprofloxacin", which belong to the class of fluoroquinolones, have demonstrated efficacy in these particular situations[12]. Resistance can potentially emerge in response to the administration of these medications[3]. Amino cyclic acid and ethionamide are both classified as second-line medicines[11]. Cycloserine and pyridoxine are medications that are generally well tolerated[5]. Injectable antibiotics such as amikacin, kanamycin, and capreomycin are employed, similar to streptomycin[12].

The adverse effects of anti-tuberculosis medications include hepatotoxicity, which is considered to be a significant concern[1]. Additional symptoms that may be present could be: nausea, jaundice and vomiting characterised by yellow skin and eye discoloration, dark coloured urine, unexplained fever and fatigue, tingling sensation and numbness in hands and feet along with joints discomfort[13].

Numerous risk factors have been proposed for the occurrence of hepatotoxicity in individuals undergoing short-term antituberculosis treatment[14]. Several factors have been identified as potential risk-factors for hepatotoxicity in pulmonary tuberculosis patients who are on anti-tuberculosis pharmacological treatment[15]. Such factors include age, extent of disease, diet history, liver disease history, hepatitis infection history as well as high alcohol consumption[5].

Hepatotoxicity is a widely recognized adverse effect associated with the drugs used for pharmacological treatment and prevention of tuberculosis[16]. The hepatotoxicity of isoniazid, which has been a long-standing cornerstone of tuberculosis medication therapy, has been established[1]. The primary medications, known as first-line pharmaceuticals, are widely regarded as the most efficacious and well-tolerated therapeutic choices for tuberculosis treatment[4]. These therapies encompass isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin[5].

The primary side effects commonly associated with anti-tuberculosis medication are hepatotoxicity, skin responses, gastrointestinal disturbances and neurological issues[9]. The occurrence of hepatotoxicity generated by anti-tuberculosis drugs is major contributor to both morbidity rates, while also compromising the efficacy of treatment[1]. Anti-tuberculosis treatment often leads to asymptomatic transaminase elevations, especially with hepatotoxic medications like isoniazid, rifampicin, and pyrazinamide which are metabolized in the liver[7]. Hepatic drug responses typically manifest within the initial two months of treatment, although they can potentially arise at any point over the course of treatment[3].

Hepatotoxicity can be detected through the use of LFTs (liver function tests), which encompass alanine-aminotransferase (ALT), aspartate-aminotransferase (AST), alkaline-phosphatase (ALK.P) and bilirubin measurements[17]. The increase in the levels of these enzymes indicates the presence of hepatotoxicity[1].

The aim of the present study was to evaluate the prevalence of hepatotoxicity in TB patients under treatment in different age groups. In addition, knowing the degree of toxicity of different combinations of anti-tuberculosis drugs.

MATERIALS AND METHODS

Study design and settings:

For the present study, ethical-approval from ERB-Ethical review board of "Shaheed Zulfiqar Ali Bhutto Medical University" was attained with a protocol number: ERB/SZABMU/330. A cross-sectional observational study was performed to assess the extent of hepatotoxicity by different drug combinations of tuberculosis pharmacological therapy. The data was collected from tuberculosis patients undergoing tuberculosis therapy from PIMS hospital Islamabad, Pakistan. The study duration was of 4 months approximately, from; March-June, 2023.

The patient profiles were examined in order to determine hepatotoxicity in individuals receiving tuberculosis treatment. The liver function test (LFT) is essential criteria for the assessment of hepatotoxicity. The primary laboratory tests conducted to assess liver function included measurements Serum-Glutamic Pyruvic- Transaminase (SGPT) or alanine-amino-

transferase (ALT), alkaline- phosphatase (ALP) along with bilirubin levels.

Based upon convenient sample technique, 100 study subjects were included in the current study, who passed the inclusion criterion.

Inclusion criterion

The tuberculosis patients who were undergoing anti-tuberculosis pharmacological therapy were included in the current study. The study subjects willing to show participation and presented an informed-consent-form (ICF) were included in the present study.

Exclusion criterion

However, the tuberculosis patients with comorbidites were excluded from the present study. Moreover, the patients undergoing any other drug therapy in addition to anti-tuberculosis drug therapy were removed from current study. Pregnant females and patients of HIV/AIDS were excluded from the study.

Data Collection form

A well structured data collection form was designed to collect data from study subjects. The data collection form gathered the demographic data of tuberculosis patients. For accessing the hepatotoxicity, the reports of liver function tests (LFTs) of patients were recorded. The study subjects' data has been kept confidential and results were not disclosed.

Statistical analysis

The data of study subjects were analyzed through SPSS version-21. Descriptive statistics was utilized to evaluate variable to generate results. Categorical variables have been presented in the form of percentage with frequencies. The p value <0.05 has been considered statistically significant.

RESULTS

Total 100 tuberculosis patients (male and female) were recruited for the present study. The study subjects were of varying age and included children as well. Among 100 patients, 49% patients were male among which 26 were hepatotoxic. Whereas, 51% patients were female, among which 29 patients presented hepatotoxicity in response to anti-tuberculosis therapy. Table 1 presents the demographics of the study subjects.

Table 1: Frequency of hepatotoxicity in patients receiving anti-tuberculosis therapy.

Variable	Categories	Frequency (N)	Hepatotoxic N (%)
Gender	Male	49	26 (53)
	Female	51	29 (56)

Table 2 indicates significant differences in cases of hepatotoxicity respective to different age groups. Most of the individuals that developed hepatotoxicity belonged to age group of 31 to 40 years. Furthermore, it is graphically represented in Figure 1. The tests performed were SGPT, ALP and Bilirubin. The major indicator of hepatotoxicity was Serum-Glutamic Pyruvic-Transaminase (SGPT). Percentage of hepatotoxicity in both male and female presents the results that the female study subjects are more prone to hepatotoxicity as compared to male study subjects. Hepatotoxicity with respect to combination therapy: The study centre administered a treatment regimen for tuberculosis (TB) that consisted of 4 medications: Isoniazid (INH), Rifampicin (RIF), Pyrazinamide (PZA) along with Ethambutanol (EMB). The comparative hepatotoxicity of RIF and INH was evaluated using liver function tests, revealing that RIF exhibits a higher level of hepatotoxicity in comparison to INH. However, the co-administration of two medications, specifically INH and RIF, demonstrated a higher incidence of hepatotoxicity in comparison to the individual drugs.

Furthermore, it was discovered that the combination therapy of isoniazid (INH), rifampicin (RIF) and pyrazinamide (PZA) presented anenhanced incidence of hepatotoxicity when compared to the combination of all four medications, namely INH, RIF, PZA as well as ethambutol (EMB). Table 3 presents the drug combination related hepatotoxicity where 'a' indicates INH, 'b' indicates RIF, 'c' indicates PZA, 'd' indicates EMB.

Table 2: Age related hepatotoxicity in TB patients.

Age (years)	Study Subjects N	Hepatotoxic patients N (%)
1-10	4	1 (25)
11-20	15	3 (20)
21-30	20	12 (60)
31-40	22	12 (54.5)
41-50	15	13 (86.6)
51-60	12	8 (66.6)
61-70	9	5 (55.5)
71-80	3	1 (33.3)

Table 3 presents the extent of hepatotoxicity in response to different drug combination of anti-tuberculosis drugs and is graphically presented in Figure 2.

Serum concentration- Liver function tests (LFTs) were performed to assess hepatotoxicity. The SGPT serves as a primary biomarker for hepatotoxicity. The standard reference range for serum SGPT is 42 IU/L. The patients who exhibit an elevation in SGPT levels of around 45% demonstrate values that fall within the range of 84 IU/L. Approximately 5% of individuals exhibit elevated serum SGPT readings that are 2 to 3

times higher than the established normal range. Furthermore, the current study presents that occurrence of hepatotoxicity might vary depending upon length of treatment.

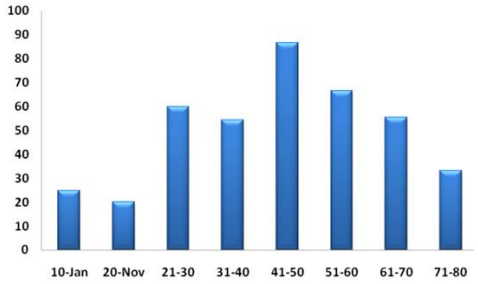

Figure 1: Age related hepatotoxicity in study subjects.

DISCUSSION

The incidence of hepatotoxicity, a significant adverse effect associated with tuberculosis therapy, exhibits variability across various countries, with rates extending from 1% to 10%[12]. The prevalence of the disorder varies based on criteria like race, ethnicity, socio-economic status along with geographical space[8]. The highest percentage of anti-tuberculosis related hepatotoxicity was observed in India, with a range of 8-10%[1]. In contrast, Western countries exhibited lower rates, with the United States having a prevalence of less than 1%, the United Kingdom at 4%, and Barcelona in Spain at 3.3%[5]. The risk factors associated with hepatotoxicity that have been reported in the literature include advanced age, paediatric age, female gender, compromised nutrition, excessive alcohol use, liver illness history, presence of hepatitis-B infection, co-infection with hepatitis B and C, extensive disease, low levels of albumin in the blood, and acetylator status[11]. Regular monitoring is necessary for patients in all disease categories, involving periodic clinical evaluations and laboratory examinations, throughout the course of treatment[15].

Table 3: Drug related hepatotoxicity.

Drug combination	Total patients (N)	Patients hepatotoxic N(%)
a	10	3 (30)
b	16	7 (43.7)
a+b	31	17 (54.8)
a+b+c	16	16 (100)
a+b+c+d	27	18 (66.7)

The current study presents that females present greater hepatotoxicity in response to anti-tuberculosis therapy as compared to male tuberculosis patients. The presence of advanced tuberculosis disease may potentially increase the risk of the tuberculosis drug induced liver injury, while it is challenging to completely eliminate the influence of variables that may complicate the relationship[18].

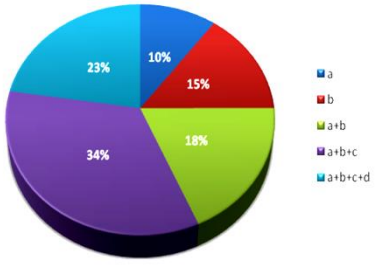

Figure 2: Anti-tuberculosis drug combination related hepatotoxicity.

Similar results were presented by a retrospective study conducted in Indonesia, presenting that drug induced hepatotoxicity tends to increase with greater number of drugs and is more common in female patients[13]. Similarly, a prospective cohort study conducted in Peshawar, Pakistan presented that anti-tuberculosis drug induced hepatotoxicity is comparatively greater in female patients as compared to male patients suffering from tubetculosis[6]. Contrarily, a prospective study conducted in Maharashtra, India presented no specific association of gender with hepatotoxicity in tuberculosis patients[1]. The current study presented that occurrence of hepatotoxicity is highest in the adults aged from 40-50 years of age. Advancing age is a significant risk for drug associated liver injury associated with tuberculosis; the research population saw a higher incidence of hepatotoxicity in patients over the age of 40 compared to their younger patients in the present study. However, the higher occurrence of liver toxicity in older individuals may be attributed to a greater frequency of concurrent medical conditions and the usage of other medications within this age demographic[19]. Similarly, the study conducted upon tuberculosis patients from India, presented that hepatotoxicity is more common in adults aged greater than 40 years[1].

In contrast, a cross sectional study conducted in Toronto, Canada presented somewhat different results i.e., age is not a contributing factor for hepatotoxicity in case of chronic liver disease patients[19]. Moreover, a cross sectional study from Sindh, Pakistan presented no significant association of age with tuberculosis therapy induced hepatotoxicity[20]. Similarly, a case report study conducted in Chennai, India presents that the incidence of severe hepatotoxicity among adults increase when rifampicin was included in a multidrug therapy regimen[21]. It has also been shown that pyrazinamide increases the likelihood or severity of hepatotoxicity[12]. Similarly, another case report conducted in Mangalagiri, India presented similar results that the extent of hepatotoxicity tends to increase with the simultaneous use of Levofloxacin with tuberculosis drugs[11]. It is recommended that patients undergo evaluation for hepatotoxicity through comprehensive assessment of medical history, thorough physical-examination and laboratory findings[22]. Additionally,

patients should be informed regarding the manifestations of hepatotoxicity, such as loss of appetite, nausea, vomiting along with abdominal pain[3]. Furthermore, patients should be educated about the precautions associated with the consumption of alcohol and hepatotoxic drugs, as well as the importance of routinely follow-up in between the treatment is suggested in patients presenting abnormal liver function tests at baseline and risk factors[23].

As per the guidelines set forth by the WHO (World Health Organization), it is deemed satisfactory to monitor patients using clinical indicators alone[19]. Routine laboratory monitoring was not advised unless there was a documented liver disease history, consistent alcohol usage along with the presence of advanced symptoms[20]. In the current study, laboratory controls were conducted exclusively on individuals with elevated liver enzymes at the onset, while patients presenting normal laboratory results and no clinical symptoms were not subjected to routine laboratory monitoring. Although INH, RIF, and PZM are recognized as hepatotoxic medications, there is still no agreement among experts regarding the specific criteria for discontinuing treatment with these treatments[24]. According to the guidelines provided by the American Tuberculosis Society (ATS), it is advised to discontinue the use of hepatotoxic medicines promptly if the levels of AST exceed 5-times the normal limit[13]. When liver enzymes exhibit a fivefold increase from the standard levels, it is recommended that you discontinue the administration of all medications[24].

In the context of used clinical setting, the presence of hepatotoxicity was taken into account when there was an elevation of serum AST and ALT levels that exceeded 3-times the upper limit of normal[23]. Additionally, an increase in serum total bilirubin levels greater than 1.5mg/dL elevation in AST or ALT levels beyond the level observed prior to treatment[11]. The specific medicine responsible for hepatotoxicity remains unidentified, and because to the potential for drug resistance, modifications to the treatment regimen are probable[24]. Consequently, in the event of hepatotoxicity development in our patients, the discontinuation of all ongoing tuberculosis medications was implemented[25]. Based on existing guidelines, in cases where drug-induced hepatitis is diagnosed, it is advised to discontinue the administration of anti-tuberculosis medications and refrain from their use until liver function tests return to normal[14]. The implementation of a novel treatment regimen should be considered after hepatotoxicity, as long as the ALT levels remain below twice the upper limit of normal[11]. In the examined cohort, the continuation of treatment occurred exclusively following the restoration of liver enzyme levels to a state of normal[7]. In current clinical setting, administration of whole drug dosages was initiated following the restoration of enzyme values in 55 out of 100 cases that experienced recurring hepatotoxicity.

Similarly, in cases when patients experience long-term and severe hepatotoxicity and are able to tolerate the medications rifampin (RIF) and isoniazid (INH), it has been indicated that extending the treatment duration to 9 months is a safer approach compared to adding pyrazinamide (PZM) to the treatment regimen[25].The (WHO) recommends a treatment regimen consisting of two months of administering isoniazid+ ethambutol+ streptomycin, following ten months of: isoniazid+ ethambutol, in cases where rifampicin is implicated[23].

If the use of isoniazid is contraindicated, it is recommended to explore a treatment regimen consisting rifampicin, pyrazinamide along with ethambutol for duration of 6-9 months[19]. However, if pyrazinamide administration is stopped prior to the completion of intensive phase, the complete duration of therapy with isoniazid + rifampicin may need to be prolonged to 9 months[25].

The current investigation mostly employs a combined therapy. The incidence of hepatotoxicity was higher in patients treated with RIF in comparison to those treated with INH. Patients with up to two months of therapy were surveyed. There have been cases of hepatotoxicity after 15 days of therapy. Several age groups were studied; with hepatotoxicity cases concentrated in the 40-60-year range. These patients took no other drugs. One disease therapy was administered to patients.

Limitations of the study

Being a single center research study, the results cannot be extrapolated to the national level. Furthermore, the sample size of the current study was not large enough so a larger population size could have provided more accurate results.

CONCLUSIONS AND RECOMMENDATIONS

Hepatotoxicity represents a prominent adverse effect associated with anti-tuberculosis medication. The findings of the current study demonstrate that female patients undergoing tuberculosis therapy imposes higher incidence of hepatotoxicity as compared to male population. The majority of the identified cases were among the age of 35 to 60 years. A small percentage, approximately 3-5% of individuals, exhibit elevated SGPT levels that exceed twice the standard range. While the remaining 50% exhibits hepatotoxicity levels that are 1-2 times higher than the standard limits. Additionally, it is evident that when the utilization of drug combinations becomes more prevalent, the likelihood of experiencing hepatotoxicity is raised.

Drawing concrete conclusions about the hazards associated with certain treatment regimens is challenging due to the utilization of diverse drug regimens in different study populations, the presence of differing definitions of hepatotoxicity, and the adoption of distinct monitoring in hepatotoxicity management. It is essential to implement rigorous monitoring of liver function tests throughout the administration of tuberculosis treatment to patients.

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AUTHOR'S CONTRIBUTION

Shahid S: writing original draft, methodology. **Ahmed F:** editing, review. **Mustafa A:** formal analysis, supervision. **Sana A:** writing, review, and editing. **Khan R:** editing, data curation. **Shahzad S:** writing, editing, data curation. **Zulfiqar A:** formal analysis, writing. **Farooq H:** data analysis, interpretations. **Abbas S:** methodology, investigation. **Razzaq T:** review. **Amjad U**: conceptualization and project. **Ali W:** initial draft of the manuscript. **Saqlain M:** data analysis and interpretations. All authors read and approved the final manuscript for publication.

DATA AVAILABILITY

Data will be made available on request.

CONFLICT OF INTEREST

The authors present no certain conflict of interest regarding present study.

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