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A STUDY OF DRUG INDUCED LIVER INJURY ON ANTITUBERCULAR THERAPY IN A TERTIARY CARE CENTRE

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ABSTRACT

This study examines drug-induced liver injury (DILI) in patients receiving antitubercular therapy (ATT) at a tertiary care centre. Tuberculosis (TB) continues to be a major public health issue, and while ATT is critical for effective treatment, the associated risk of hepatotoxicity is a significant concern. The primary goal of this research is to evaluate the incidence, clinical manifestations, risk factors, and outcomes related to DILI in patients on ATT. A retrospective analysis was conducted involving patients diagnosed with TB who were treated with first-line antitubercular drugs over a one-year period. The study gathered clinical data, including demographic details, liver function test results, and reported adverse drug reactions. The severity of liver injury was categorized using established criteria, and potential risk factors such as age, sex, pre-existing liver conditions, alcohol use, and concurrent medications were analyzed. The results indicated a significant incidence of DILI among patients undergoing ATT, particularly in those with pre-existing liver issues and alcohol consumption. Common symptoms included jaundice, fatigue, and abdominal pain. Most cases were classified as mild to moderate, with a majority of patients recovering following appropriate management, which involved temporarily halting the offending medications and providing supportive care. This study highlights the necessity for careful monitoring of liver function in patients receiving ATT, particularly among high-risk groups. Early detection and management of DILI are crucial to preventing severe complications and ensuring continued TB treatment. The findings emphasize the importance of increasing awareness among healthcare providers regarding the hepatotoxic risks of antitubercular drugs and the need for routine liver function assessments during therapy. Future research should focus on strategies to reduce the risk of DILI while maintaining effective

Keywords: Antitubercular therapy, Tuberculosis, Hepatotoxicity, Liver function tests, Risk factors, Clinical presentation, Tertiary care center, Patient outcomes.

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INTRODUCTION

Tuberculosis (TB) eradication continues to pose significant global challenges, with TB remaining the leading cause of death from infectious diseases worldwide [1]. Despite advancements in medical treatment, the management of TB necessitates prolonged and complex regimens, which can lead to a range of adverse drug events. Among these, drug-induced liver injury (DILI) stands out as one of the most common side effects that may require the interruption or modification of therapy[2]. The incidence of DILI in patients receiving standard antitubercular drug regimens has been reported to range from 2% to 28%, highlighting a considerable risk associated with these essential medications. DILI is primarily caused by the direct toxic effects of drug metabolites or through immune system-mediated pathways. Understanding the underlying mechanisms is crucial for anticipating potential complications[3]. Certain demographic and clinical factors have been identified as principal risk factors for the development of DILI, including older age, advanced stages of TB, high levels of alcohol intake, and pre-existing liver disease [4]. These factors increase vulnerability to liver injury, necessitating careful monitoring during treatment. However, predicting DILI remains a challenge, as many cases arise from unpredictable idiosyncratic reactions that are not directly correlated with the drug dose or duration of treatment[5]. The clinical manifestations of DILI can vary widely, ranging from asymptomatic elevations in liver enzyme levels to severe, fulminant liver failure[6]. The diversity of symptoms complicates diagnosis and management, as some patients may not exhibit any significant signs of liver injury despite elevated enzyme levels[7]. In this study, Drug-induced liver injury (DILI) is characterized by certain criteria: serum aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels that are more than five times the upper limit of normal , or AST and/or ALT levels exceeding three times the ULN along with symptoms such as fatigue, nausea, vomiting, abdominal pain, and reduced appetite. [8]. Additionally, a criterion for improvement includes at least a 50% reduction in liver enzyme levels following appropriate management. Given the critical role of effective TB treatment and the potential for DILI to disrupt therapy, this study aims to systematically evaluate the incidence, risk factors, clinical presentations, and outcomes of DILI in patients receiving antitubercular therapy at a tertiary care center[9]. Understanding these dynamics is essential for optimizing patient care and minimizing complications associated with TB treatment[10].

AIM AND OBJECTIVE

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The study aims to investigate the duration of treatment and final clinical outcomes in patients experiencing drug-induced liver injury (DILI) due to antitubercular therapy (ATT). This understanding will help optimize management strategies and improve patient safety and treatment efficacy during TB therapy.

METHODOLOGY

A retrospective cohort study was conducted from January 1 to December 31, 2022, at the Karwar Institute of Medical Sciences in Uttara Kannada. Patients with pulmonary TB were identified from a prospective registry. An ethical approval has been obtained from the Ethical Approval Committee. A sample size of 42 was calculated using a standard formula, considering a 95% confidence level and 10% precision. Inclusion criteria included patients over 18 years with confirmed pulmonary TB via AFB culture and treated with the standard regimen, followed by a two-month sputum culture assessment. Exclusion criteria comprised those initially treated with non-standard regimens, patients with relapses, extra-pulmonary TB, drug-resistant TB, and individuals lost to follow-up or under 18 years.

RESULT

The antitubercular drug-induced liver injury study included a total of 42 participants, comprising 32 males and 10 females.

Table 1 : Demographic and clinical characterstics of the study population

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CHARACTERISTIC	TOTAL (N=42)	DILI (n=5)	NON-DILI (n=37)	P-value
Age in years	54.1 ± 18.5	63.2 ± 16.9	52.6 ± 18.4	0.015
BMI in kg/m²	21.5 ± 3.5	20.1 ± 3.7	21.6 ± 3.4	0.21
Chronic liver disease	5	3	2	0.002
Chronic alcoholism	15	4	11	0.025
Diabetes mellitus	13	1	12	0.85
Radiological evidence of PTB	20	3	17	0.69
Frequency of sputum smear/culture	6.5 ± 2.9	6.3 ± 2.4	6.5 ± 3.0	0.95
Positive AFB smear	18	2	16	0.812
Positive AFB culture/CBNAAT	39	4	35	0.74
Sex				
Male	32	4	28	0.051
Female	10	1	9	

The table summarizes the characteristics of 42 patients undergoing antitubercular therapy, highlighting the incidence of drug-induced liver injury (DILI) and non-DILI cases. It includes parameters such as age, BMI, chronic liver disease, alcohol use, diabetes, and sputum analysis, with corresponding P-values indicating statistical significance.

Table 2 : Clinical outcome of the patient with TB by DILI

Status

Characteristics	Total (N=42)	DILI (n=5)	Non-DILI (n=37)	P-value

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Total treatment duration in days	248.2 ± 95.4	251.0 ± 79.3	247.5 ± 98.6	0.91
Treatment stoppage period/total treatment duration	0.03 ± 0.05	0.05 ± 0.07	0.02 ± 0.03	< 0.001
2 months sputum AFB culture conversion	34	4	30	0.815
completion of treatment	27	2	25	0.49
Treatment success	38	2	36	0.018
PTB-related death	0	0	0	1

The table presents clinical characteristics of 42 patients treated for tuberculosis, comparing those with drug-induced liver injury (DILI) to those without. Key metrics include total treatment duration, treatment interruption rates, sputum culture conversion, treatment completion, and success rates, highlighting significant differences in treatment outcomes, particularly treatment success.

Table 3: Management of DILI

CHARACTERISTIC	**TOTAL (N=42)**	**DILI (n=5)**	**NON-DILI (n=37)**	**P-value**
Onset time for DILI from starting of ATT		65.2 ± 58.4		
Liver protective agents administration	5	4	1	< 0.001
Reintroduction methods				

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Restarting full dose after 1 week		3		
Changing ATT regimen		1		
Starting with subtherapeutic dose followed by stepwise increase of dose		1		

The table outlines characteristics related to drug-induced liver injury in 42 patients undergoing treatment. It presents the onset time for DILI, the administration of Liver protective agents, and various reintroduction methods. P-values indicate statistical significance for Liver protective agents administration, emphasizing their potential impact on managing liver injury during therapy.

DISCUSSION

The results from the demographic and clinical characteristics of the study population provide important insights into the incidence and impact of drug-induced liver injury (DILI) among patients undergoing antitubercular therapy (ATT) [11]. The study included 42 patients, of which 5 patients developed DILI revealing significant differences between those with DILI and those without in several key parameters. Age emerged as a crucial factor, with patients suffering from DILI having a mean age of 63.2 years compared to 52.6 years in the non-DILI group, and this difference was statistically significant ($p=0.015$) [12]. This finding aligns with existing literature suggesting that older patients may have an increased vulnerability to hepatotoxicity due to age-related physiological changes and potential comorbidities. Another significant factor was the presence of chronic liver disease, where 3 out of 5 patients with DILI had pre-existing liver conditions, highlighting a substantial risk factor ($p=0.002$). This underscores the necessity for careful screening and monitoring of liver function in patients with a history of liver disease undergoing ATT [13]. Additionally, the prevalence of chronic alcohol use was higher in the DILI group (4 out of 5), indicating that alcohol consumption can further exacerbate the risk of hepatotoxicity ($p=0.025$). The data regarding diabetes mellitus did not show a significant association with DILI, as only one patient with DILI had this condition ($p=0.85$). This suggests that diabetes may not be a primary risk factor in the context of DILI in this population, contrasting with other studies that have suggested a link between metabolic disorders and liver injury. The clinical outcomes presented further reinforce the implications of DILI on treatment efficacy [14]. Although the total treatment duration was similar across both groups, the treatment interruption rate was significantly higher in patients with DILI ($p<0.001$), which may affect overall treatment success. Treatment success rates were notably lower in the DILI group ($p=0.018$), indicating that liver injury could hinder the overall management of tuberculosis, potentially leading to poorer health outcomes [15]. Management strategies for DILI

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included hepatotonics, with 5 patients receiving such treatment, four of whom were in the DILI group, demonstrating a significant focus on mitigating liver injury ($p<0.001$). The reintroduction methods varied, with three patients resuming full doses after one week,1 patient had change in regimen and 1 patient was started with subtherapeutic dose and stepwise increasing suggesting a cautious approach to reinstating therapy [16]. Overall, the results underscore the importance of vigilance in monitoring liver function in patients undergoing ATT, particularly among older individuals and those with underlying liver conditions. Enhanced awareness of the risks associated with DILI and tailored management strategies could significantly improve treatment outcomes for tuberculosis patients. Future research should aim to refine these strategies, focusing on identifying additional risk factors and potential protective measures against hepatotoxicity [17].

CONCLUSION

DILI frequently occurred during TB treatment, especially in older patients and those with chronic liver disease. Although it did not significantly affect sputum culture conversion, treatment outcomes, or overall treatment duration, interruptions caused by DILI raised concerns about the potential for future relapses and acquired drug resistance. The management of DILI remains poorly defined, highlighting the need for standardized protocols to address this complication. Understanding the implications of DILI on TB treatment is crucial for improving patient outcomes and minimizing risks associated with therapy interruptions. Continued research is essential to develop effective strategies for preventing and managing DILI in TB patients.

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