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"A STUDY OF DRUG-INDUCED LIVER INJURY AND LFT MONITORING IN PULMONARY TUBERCULOSIS PATIENTS REGISTERED WITH NTEP"

General Medicine

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ABSTRACT

Introduction- Tuberculosis (TB) remains a major health challenge in India, with the highest global burden. Anti-tuberculosis therapy (ATT) under NTEP has improved outcomes but is associated with Drug-Induced Liver Injury (DILI). First-line drugs like isoniazid, rifampicin, and pyrazinamide can cause hepatotoxicity, especially in high-risk groups. DILI may lead to treatment interruption, non-adherence, and drug resistance. Regular monitoring of Liver Function Tests (LFTs) aids in early detection and management of hepatotoxicity. This study evaluates the incidence of DILI and the role of LFT monitoring in pulmonary TB patients on ATT. **Objective:** To evaluate liver function test (LFT) values in pulmonary tuberculosis patients undergoing anti-tubercular therapy (ATT) and assess their correlation with hepatotoxicity. **Materials And Methods** - In our study 100 patient with pulmonary TB ,who met the inclusion and exclusion criteria were selected from the medicine wards and OPD at department of internal medicine. LFT was measured at baseline and a week after initiating first line ATT as per NTEP. **Results -** Among 100 pulmonary tuberculosis patients initiated on anti-tuberculosis therapy (ATT).After one week of ATT 15 (15%) developed Drug-Induced Liver Injury (DILI) as per WHO criteria. The injury patterns included mixed (40%), hepatocellular (33.3%), and cholestatic (26.7%). Severity grading revealed that 11 patients (73.3%) had Grade 3 (severe) DILI, while 2 patients each (13.3%) had Grade 1 (mild) and Grade 2 (moderate) DILI. No cases progressed to Grade 4 (life-threatening) or acute liver failure. Early monitoring and timely intervention likely prevented severe clinical outcomes. **Conclusion–** DILI is a common occurrence during the course of anti-TB treatment. Monitoring of LFTs can detect the liver injury and helps in the management and serious prevention of ATLI. Most patients show tolerance to anti-TB drugs and get adjusted after transient rise in liver enzymes.

KEYWORDS

INTRODUCTION

Tuberculosis (TB), one of the oldest known diseases caused by Mycobacterium tuberculosis, remains a major global health issue. In 2023, it caused 10.8 million cases and 1.25 million deaths worldwide. India, with the highest TB burden, accounted for 26% of global cases but has made progress, reducing incidence from 237 to 195 per 100,000 population since 2015[1].

Advancements in drug-induced liver injury (DILI) monitoring have identified genetic predispositions affecting anti-tuberculosis drug-induced liver injury (ATLI). Newer Researches highlights that NAT2 and CYP2E1 polymorphisms significantly influence isoniazid metabolism, increasing the risk of hepatotoxicity. Recent studies have also explored novel biomarkers such as microRNAs and HMGB1 for early detection of liver injury[2].

Hepatotoxicity remains a major concern in TB treatment, particularly among high-risk populations. Factors such as advanced age, malnutrition, and co-existing infections (HBV, HCV, HIV) significantly increase the risk of liver injury. Preventive strategies emphasize regular monitoring of liver function tests (LFTs), the use of hepatoprotective agents, and necessary dose modifications to mitigate adverse effects[3].

Drug-induced liver injury (DILI) is an important adverse effect of anti-tuberculosis (TB) drugs. First-line anti-TB drugs including isoniazid, rifampicin, and pyrazinamide have been shown to have potential hepatotoxicity. Anti-TB drug-induced liver injury (ATLI) can range from asymptomatic elevation of aminotransferase to severe hepatotoxicity, or in some cases hepatic failure. Prevention of ATLI is crucial for patient safety and the control of TB[4].

Regular LFT monitoring is key to preventing ATLI, but current data on hepatotoxicity risks is limited. This study was conducted due to the lack of sufficient evidence[5].

Objective

To evaluate liver function test (LFT) values in pulmonary tuberculosis patients undergoing anti-tubercular therapy (ATT) and assess their correlation with hepatotoxicity.

MATERIALS AND METHODS

- The study included 100 patients from the OPD and IPD of Basaveshwar Teaching & General Hospital, Kalaburagi, between October 2023 and May 2024. Data were collected using a structured proforma, followed by clinical examination and relevant investigations.
- Data was entered into Microsoft excel data sheet and analyzed using SPSS V25. Chi- square test, Fisher exact test, Independent t-test will be applied. Sensitivity and specificity are calculated. $P<0.05$ is considered as statiscally significant.

Inclusion Criteria:

1) Patient's diagnosed as having an active TB infection,which was verified by a positive acid-fast stain(AFB), a nucleic acid amplification test(NAAT), or a Mycobacterium TB culture, those who are on 1st line ATT.
2) Age more than 18 years and any gender.

Exclusion Criteria:

1) Patients having co-existing liver disorders and infections.
2) Infected by Non-TB bacterium or Multi-drug resistance- TB , extensively drug resistant TB patients.
3) Pregnant and lactating females

RESULTS

Age distribution in the current study, ranging from 18 to 86 years. The majority of cases fell within the 31-50 age group, accounting for 42.0% of the total. Following this, 30.0% of cases were in the 51-70 age group, and 21.0% were in the 18-30 age group. The mean age of cases was calculated to be 46.23 years.The current study, male cases were predominant at 66 (66.0%) compared to female cases at 34 (34.0%). The male to female ratio was 1.94:1.

The findings of the study, which observed 100 cases of pulmonary tuberculosis (PTB). The results show that 58% of the cases had no identified habits, while 28% were found to be smokers, 19% were alcohol consumers, and 9% were tobacco users. These statistics highlight the various habits prevalent among PTB patients, shedding light on potential risk factors associated with the disease.

Table No.1: Correlating The Values Of Hepatotoxicity

Variables	At admission without ATT	1 week after ATT	T-test values, P-value & significance
	Mean ± SD	Mean ± SD	
Total Bilirubin	0.91 ± 0.35	1.23 ± 0.73	t = -4.527, P = 0.000, HS
DB	0.43± 0.21	0.57 ± 0.38	t = -3542, P = 0.001, HS
IB	0.51 ± 0.41	0.73 ± 0.88	t = -2.368, P = 0.020, S
SGOT	30.91 ± 12.04	82.77 ± 112.40	t = -4.707, P = 0.000, HS
SGPT	26.78 ± 12.07	87.40 ± 129.32	t = -4.751, P = 0.000, HS
ALP	88.50 ± 28.12	115.32 ± 84.43	t = -3.025 P = 0.003, HS
TP	6.57 ± 0.80	6.41 ± 0.85	t = 3.099, P = 0.003, HS
ALB	3.31 ± 0.56	3.06 ± 0.50	t = 5.557, P = 0.000, HS
GLB	3.20 ± 0.65	3.34 ± 0.59	t = -2.318, P = 0.023, S
A/G ratio	1.05 ± 0.27	0.90 ± 0.19	t = 6.248, P = 0.000, HS

Table 1 from the Study demonstrates that the liver function test (LFT) values of mean Total bilirubin, Direct Bilirubin (DB), Indirect Bilirubin (IB), Serum Glutamic Oxaloacetic Transaminase (SGOT), Serum Glutamic Pyruvic Transaminase (SGPT), Alkaline Phosphatase (ALP), and Globulin (GLB) significantly increased following the administration of Anti-Tuberculosis Treatment (ATT) due to hepatotoxicity. These findings are statistically highly significant (P<0.001).

Conversely, the mean values of Total Protein (TP), Albumin (ALB), and the Albumin/Globulin (A/G) ratio were significantly decreased after the ATT treatment due to hepatotoxicity. Again, these results are statistically highly significant (P<0.001).

Among the 15 patients who met the WHO criteria for DILI (hepatocellular, cholestatic, or mixed pattern given in the table no.2):

Table No.2 Pattern of Liver Injury

Injury Pattern	Number of Patients
Mixed	6
Hepatocellular	5
Cholestatic	4

Table No.3 Severity Grading Among WHO-Classified DILI Cases

DILI Severity Grade	Number of Patients
Grade 3 – Severe	11
Grade 2 – Moderate	2
Grade 1 – Mild	2

This indicates that the majority of hepatotoxicity cases during the first week of ATT are biochemically significant yet clinically silent. These findings underscore the necessity of routine biochemical monitoring, as most patients do not exhibit overt symptoms despite enzyme elevations.

This analysis underscores the importance of routine LFT monitoring during ATT, as a notable subset of patients developed significant hepatic injury within the first week of therapy.

There was no evidence of acute liver failure among the study participants.

Management of DILI in the Present Study

- **Grade 1 (Mild) DILI (2 patients),Grade 2 (Moderate) DILI (4 patients):**
- Continued ATT with close monitoring of liver function every 3–5 days.
- Patients were advised on symptom vigilance for early signs of liver injury (jaundice, nausea, anorexia).
- No change in drug regimen unless enzyme levels increased or symptoms worsened.

- **Grade 3 (Severe) DILI (11 patients):**
- Immediate withdrawal of suspected hepatotoxic drugs (isoniazid, rifampicin, pyrazinamide).
- Supportive care was initiated including hydration, nutritional support, and symptom management.
- ATT was reintroduced stepwise once liver parameters normalized, typically starting with ethambutol and streptomycin, followed by isoniazid and rifampicin under supervision.
- Pyrazinamide was not reintroduced in most cases due to its higher hepatotoxic potential.

No cases of Grade 4 (Life-threatening DILI) or acute liver failure were observed in this study.

DISCUSSION

The integration of CBNAAT in our study not only confirmed MTB diagnosis but also provided a reliable assessment of Rif sensitivity, which is pivotal given rifampicin's cornerstone role in TB treatment regimens. The absence of Rif resistance in our cohort is encouraging, as rifampicin resistance is a hallmark of MDR-TB, which complicates treatment and increases hepatotoxicity risks due to alternative drug regimens[6].

Chandra A et al.'s[7] study observed significant fluctuations in liver function parameters during treatment. SGPT levels showed a rise in mean values from the 2nd week (SD ±17.56) to the 4th week (SD ±35.37), followed by a decline in the 6th week (p< 0.001). Similarly, SGOT levels increased from the 2nd week (SD ±14.85) to the 6th week (SD ±26.18) before falling in the 8th week (p< 0.0001).

The study found that 83.3% of patients had elevated SGPT levels, while 71.1% had elevated SGOT levels. Both enzymes were elevated in 66.7% of cases. Severe elevation (>5 times normal) was rare (1.75%), and 4.38% of patients with elevations >3 times normal were symptomatic.Most liver enzyme elevations occurred in the 2nd and 4th weeks of ATT in our study. Despite hepatitis in 5 cases, full-dose ATT was continued without recurrence, showing outcomes comparable to hepato-safe regimens[8].

The incidence of DILI was comparable (~12–15%). However, the pattern of liver injury varied: Mixed injury was predominant in the current study, whereas hepatocellular injury was more common in the study by Taneja et al. Notably, no cases of acute liver failure were observed in the present study, while Taneja et al. reported 2 cases. This suggests that early monitoring and appropriate management may help prevent progression to severe outcomes[9].

Follow-up data showed that SGPT and SGOT levels remained elevated in a significant number of patients over multiple follow-ups, with the highest percentage of cases recorded during the first follow-up (SGPT: 39.5%, SGOT: 33.3%), gradually decreasing over time. This indicates a trend of enzyme elevation early in treatment, with a decline over subsequent follow-ups[10].

CONCLUSION:

- CBNAAT is highly effective for diagnosing MTB and determining rifampicin sensitivity, even in AFB-negative cases.
- ATT is associated with significant hepatotoxicity, evidenced by altered LFT parameters, emphasizing the need for regular LFT monitoring.
- Early detection of hepatotoxicity through LFT monitoring can help mitigate complications and improve treatment adherence.

Limitations:

- The study was conducted on a relatively small sample size (n=100), limiting generalizability.
- The study did not evaluate long-term outcomes or the impact of hepatotoxicity on treatment success rates.
- Absence of control group for comparative analysis.
- Only baseline and post-ATT LFT values were analyzed; intermediate monitoring during treatment was not included.

Recommendations:

- Mandate LFT monitoring before, during, and after ATT.
- Train healthcare providers to identify and manage hepatotoxicity early.

Future Research:

- Conduct larger multicenter studies on ATT-induced hepatotoxicity.
- Study the impact of habits, comorbidities, and genetics on liver toxicity risk.

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