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Original Research Article

CLINICAL SPECTRUM OF DRUG-INDUCED LIVER INJURY IN A TERTIARY CARE HOSPITAL

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Abstract

Background: Drug-induced liver injury is a major cause of jaundice. It ranges from asymptomatic biochemical LFT to acute liver failure. Understanding the clinical spectrum and outcomes associated with DILI is essential in tertiary care hospital settings, where patients often have complex profiles and multiple comorbidities. This study aimed to explore the clinical spectrum, patterns, and outcomes of drug-induced liver injury in patients admitted to a tertiary care hospital. **Materials and Methods:** This prospective observational study included 50 patients who met the DILI criteria based on a history of drug exposure and subsequent liver injury and were categorized into hepatocellular, cholestatic, and mixed patterns of liver injury. Data on jaundice type, ICU admission, comorbid conditions, and patient outcomes were analysed. The inclusion criteria included patients with suspected DILI, while those with recent ethanol use, positive viral serology, or toxin-induced liver injury were excluded. **Result:** Among the 50 patients, the leading causes of DILI were Complementary and Alternative Medicines (44%) and anti-tuberculosis therapy (36%). Most of the patients with CAMS (90.9%) had chronic liver disease. Hepatocellular injury was predominant in CAMS (81.8%), whereas acute on chronic liver failure occurred in (9.1%) of the CAMS cases. Patient admissions revealed that 36.4% of patients with CAMS required ICU care, with a mortality rate of 9.1%. Notably, 88.9% of ATT patients achieved full recovery, highlighting the significant variability in outcomes based on the causative agent. **Conclusion:** This study highlights the significant role of CAMS and ATT as primary contributors to DILI, with CAMS posing a high risk of worsening liver function in patients with CLD.

INTRODUCTION

Drug-induced liver injury (DILI) is characterized by liver damage resulting from exposure to various pharmaceuticals, herbal remedies, or other xenobiotics, following the exclusion of alternative causes.[1] Diagnosing DILI, particularly the idiosyncratic (unpredictable) form, is challenging for hepatologists because of the vast array of medications, herbs, and dietary supplements that may have hepatotoxic effects, coupled with its ability to manifest in varied clinical and pathological forms.[2] This complexity is further compounded by the absence of definitive biomarkers, making it crucial to maintain a high level of clinical suspicion and carefully rule out other potential liver diseases.[3]

The absence of specific biomarkers further complicates its diagnosis, necessitating increased clinical vigilance and the thorough exclusion of alternative liver disease aetiologies. It is essential to understand this classification along with intrinsic DILI. Intrinsic DILI is typically dose-dependent and predictable, often manifesting rapidly (within hours to days) in a large subset of exposed individuals.[4] In contrast, idiosyncratic DILI is generally dose-independent, although it often requires a minimum dose of 50 to 100 mg/day. It occurs unpredictably in a small fraction of exposed individuals, with a latency period ranging from days to weeks. While both forms share overlapping pathogenic mechanisms, they diverge significantly in their triggering factors, particularly in drug lipophilicity and metabolic biotransformation. Acetaminophen toxicity is a prime example of intrinsic DILI, being the leading cause of acute liver failure, accounting for over 50% of ALF cases.[5]

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The clinical presentations of drug-induced liver injury (DILI) are diverse, ranging from asymptomatic cases, which are often incidentally detected through elevated liver enzymes, such as ALT and AST, to more severe conditions. Patients may experience acute hepatitis, which manifests with symptoms such as jaundice, fatigue, nausea, and abdominal discomfort.[6] Cholestatic injury can occur, characterized by pruritus, jaundice, and elevated alkaline phosphatase levels. In some cases, a mixed hepatocellular-cholestatic pattern is observed, combining the features of both hepatocellular damage and cholestasis. Severe instances of DILI can lead to ALF, which may progress to encephalopathy, coagulopathy, and multi-organ failure, with acetaminophen toxicity being a common cause.[7] Hepatic failure is a common type of organ dysfunction seen in critically ill patients and significantly contributes to increased morbidity and mortality.

In certain instances, DILI can progress to chronic liver damage, where persistent liver dysfunction can lead to fibrosis or cirrhosis, especially if the offending agent is not promptly identified or discontinued. This chronic progression underscores the importance of early recognition, as continued exposure to hepatotoxic agents can exacerbate liver injury.[8] The management of liver injury in such cases presents a substantial challenge that requires a multidisciplinary approach. This investigation aimed to enhance early detection, improve diagnostic accuracy, and develop effective strategies for the prevention and management of DILI.

Aim

This study aimed to explore the clinical spectrum of drug-induced liver injury, focusing on identifying the range of clinical presentations, understanding the underlying mechanisms, and identifying the risk factors that contribute to susceptibility.

MATERIALS AND METHODS

This prospective observational study was conducted on 50 patients with a history of offending drugs who met the DILI criteria at a tertiary care hospital in Thoothukudi Govt Medical College. Patients were categorized based on liver injury as having hepatocellular, cholestatic, or mixed-pattern jaundice. The patterns of hepatitis, ICU stay, and outcomes were studied. Informed consent was obtained from all the patients who participated in the study and their willingness to participate.

Inclusion criteria

Patients meeting the DILI criteria and with a history of offending drugs were included in the study.

Exclusion criteria

Patients with recent ethanol intake, positive viral serology, and toxin-induced liver injury were excluded from the study.

All patients were informed of the study design at the time of enrolment, and detailed consent regarding their willingness to participate was obtained. The study protocol was presented by the institutional ethics committee, and ethical committee clearance was obtained and enclosed.

RESULTS

Of the 50 patients, 22 patients (44%) had the primary cause of drug-induced liver injury (DILI) associated with Complementary and Alternative Medicines (CAMS), followed by 18 patients (36%) with anti-tuberculosis therapy (ATT) and 7 patients (14%) with anti-epileptic drug (AED)-induced DILI, Methotrexate (MTX) accounted for 2 patients (4%), and only 1 patient (2%) had anti-cancer treatments associated with DILI [Table 1].

Of the 22 patients with CAMS-associated DILI, 20 (90.9%) had chronic liver disease (CLD) and 2 (9.1%) had rheumatoid arthritis (RA) [Table 2].

Of the patients categorized based on the causes of drug-induced liver injury (DILI), 24 (54.5%) were associated with CAMS. Specifically, 8 (33.3%) patients were admitted to the ICU, 14 (58.3%) were admitted to the inpatient ward, and 2 (8.3%) were treated in the outpatient department. Of the 18 (40.9%) patients with ATT-related DILI, 2 (11.1%) were admitted to the ICU, 14 (77.8%) were admitted to the inpatient ward, and 2 (11.1%) were treated on an outpatient basis.

Among patients who had AED-induced DILI, 7 (15.9%) were admitted, with 2 (28.6%) requiring ICU admission, 4 (57.1%) managed in the ward, and 1 (14.3%) receiving outpatient care. Among the patients affected by MTX, only 2 (4.5%) were reported, and both patients (100%) were admitted to the inpatient ward and none in the ICU or outpatient settings. For patients with anti-cancer treatment-induced DILI, 1 (2.3%) patient was documented who was treated in the inpatient ward [Table 3].

Regarding the pattern of jaundice, 18 (81.8%) patients experienced hepatocellular injury after exposure to CAMS, followed by 12 (66.7%) patients in the ATT group, 3 (42.9%) in the AED group, 1 (50%) in the MTX group, and none in the anticancer therapy group. Cholestatic jaundice was observed in 2 (11.1%) patients in the ATT group and 2 (28.6%) in the AED group. Mixed-type liver injury was reported in 4 (18.2%) patients using CAMS, 4 (22.2%) in the ATT group, 2 (28.6%) in the AED group, 1 (50%) in the MTX group, and 1 (100%) in the anti-cancer group [Table 4].

HCLF was observed in four patients (18.2%) exposed to CAMS. ALF occurred in 10 (45.5%) patients in the CAMS group, followed by 2 (11.1%) in the ATT group and 1 (14.3%) in the AED group. Acute on chronic liver failure was reported in 2 (9.1%) patients using CAMS, 3 (16.7%) in the ATT group, 1 (14.3%) in the AED group, 2 (100%) in the MTX group, and 1 (100%) in the anti-cancer therapy group. Acute hepatitis was observed in 8 (36.4%) patients in the CAMS group, 8 (44.4%) in the ATT group, and 3 (42.9%) in the AED group. Cholestasis was present

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in four (22.2%) patients in the ATT group and two (28.6%) in the AED group, with no cases reported in the CAMS, MTX, or anticancer therapy groups. DRESS syndrome was noted in only 1 (5.6%) in the ATT group [Table 5].

Death occurred in 2 (9.1%) patients in the CAMS group, with none reported in the ATT, AED, MTX, or anti-cancer groups. 3 (13.6%) patients in the CAMS group required ICU stays of 3 days to 1 week, 2 (11.1%) in the ATT group, and 1 (14.3%) in the AED group. Longer ICU stays of > 1 week were observed in 3 (13.6%) patients using CAMS, with no such cases in the ATT, AED, MTX, or anti-cancer groups. Chronic hepatitis developed in 12 (54.5%) patients in the CAMS group, 1 (14.3%) in the AED group, and none in the other groups. Full recovery was reported in 2 (9.1%) patients in the CAMS group, 16 (88.9%) in the ATT group, 5 (71.4%) in the AED group, 2 (100%) in the MTX group, and 1 (100%) in the anti-cancer therapy group [Table 5].

Table 1: Causes of DILI.

		No. of patients (%)
Causes of DILI	CAMS	22 (44%)
	ATT	18 (36%)
	AED	7 (14%)
	MTX	2 (4%)
	Anti-cancer	1 (2%)

Table 2: Causes in CAMS

		No. of patients (%)
Causes of CAMS	CLD	20 (90.9%)
	RA	2 (9.1%)

Table 3: Distribution of patient admissions by unit based on treatment type

Admission	ICU	Ward	OP
CAMS	8 (36.4%)	14 (63.6%)	0
ATT	2 (11.1%)	14 (77.8%)	2 (11.1%)
AED	2 (28.6%)	4 (57.1%)	1 (14.3%)
MTX	0	2 (100%)	0
Anti-cancer	0	1 (100%)	0

Table 4: Distribution of jaundice patterns by treatment type

Pattern of jaundice	Hepatocellular	Cholestatic	Mixed
CAMS	18 (81.8%)	0	4 (18.2%)
ATT	12 (66.7%)	2 (11.1%)	4 (22.2%)
AED	3 (42.9%)	2 (28.6%)	2 (28.6%)
MTX	1 (50%)	0	1 (50%)
Anti-cancer	0	0	1 (100%)

Table 5: Distribution of hepatitis patterns by treatment type

PATTERN OF HEPATITS	ACLF	ALF	ACUTE LIVER INJURY	ACUTE HEPATITS	CHOLESTATIS	DRESS
CAMS	4 (18.2%)	10 (45.5%)	4 (18.2%)	8 (36.4%)	0 (0.0%)	0 (0.0%)
ATT	0 (0.0%)	2 (11.1%)	3 (16.7%)	8 (44.4%)	4 (22.2%)	1 (5.6%)
AED	0 (0.0%)	1 (14.3%)	1 (14.3%)	3 (42.9%)	2 (28.6%)	0 (0.0%)
MTX	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (100.0%)	0 (0.0%)	0 (0.0%)
ANTI CANCER	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)	0 (0.0%)

Table 6: Distribution of patient outcomes in DILI by treatment type

Outcome of DILI	Death	3 days to 1 week ICU stay	>1 week ICU stay	Chronic hepatitis	Recovered
CAMS	2 (9.1%)	3 (13.6%)	3 (13.6%)	12 (54.5%)	2 (9.1%)
ATT	0	2 (11.1%)	0	0	16 (88.9%)
AED	0	1 (14.3%)	0	1 (14.3%)	5 (71.4%)
MTX	0	0	0	0	2 (100%)
Anti-cancer	0	0	0	0	1 (100%)

DISCUSSION

DILI presents with a diverse array of clinical symptoms, from mild liver enzyme elevations to life-threatening liver failure, making timely diagnosis complex.[9] In tertiary care settings, where patients often have multiple comorbidities and are exposed to various drugs, the identification of DILI becomes even more difficult.[10] Apart from paracetamol overdose, most cases of drug-induced liver injury (DILI) observed in clinical practice are predominantly idiosyncratic. This is because only a small subset of patients exposed to these medications develop liver injuries. Often, the underlying mechanism of this idiosyncrasy involves immune-mediated responses, which are frequently linked to

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genetic predispositions, particularly variations in human leukocyte antigen (HLA) genes.[11]

Most patients experience DILI due to complementary and alternative medicines (CAMS) followed by anti-tubercular therapy (ATT). Only a few patients had methotrexate- and anti-cancer drug-induced liver injury. This was compared with the results of the study conducted by Abid et al. (2020). In their study, anti-tuberculosis drugs (ATDs) were found to be the most common category of drugs causing DILI.[12]

The study reported by Andrade et al. (2005) suggested that the anti-infective group of drugs, namely, amoxicillin clavulanate accounting for 12.8%, was more frequently implicated in the whole series in their study.[13] Chalasani N et al. (2015) conducted a study and reported that most of the patients in their study had nitrofurantoin (25%) or minocycline (17%) associated with DILI. They also reported that only 1% had experienced concomitant severe skin reactions implicated by lamotrigine, azithromycin, carbamazepine, moxifloxacin, cephalexin, diclofenac, and nitrofurantoin.[14]

During admission, patients who all had DILI in our study were admitted to the inpatient ward, followed by the intensive care unit, and only very few patients were treated in the outpatient department. This was compared with the results of a study conducted by Valle et al. (2006). They conducted a study on 1164 patients with drug-induced liver disease. They reported that 3.3% of them were referred for evaluation to the outpatient clinic whereas 3% had a follow-up after hospitalization of drug-induced liver injury.[15] Also, the study done by Abid et al. (2020) reported that 26.5% of patients had experienced in-hospital mortality and 35.93% of patients had experienced prolonged hospital stay (> 5 days).[12]

In our study, the majority of the patients experienced chronic liver disease and the least number of patients had rheumatoid arthritis (RA) and DILI because of CAMS. Based on the jaundice pattern, the majority of patients had hepatocellular jaundice, followed by mixed-type jaundice, and only a few patients had cholestatic jaundice in all types of drug-induced liver injury. Valle D et al. (2006) reported that 48% of patients had a hepatocellular pattern, 40% of patients had cholestatic and only 12% of patients had mixed patterns of jaundice in all types of DILI in their study.[15] A study conducted by Abid A et al. (2020) revealed that the pattern of liver injury was majorly hepatocellular in 25.1%, cholestatic in 56.17%, and mixed in 18.72% of patients.[12]

Based on the hepatitis pattern in our study, most patients had acute hepatitis, followed by acute on chronic liver failure, and only a few patients had liver injury in all types of drug-induced liver injury. Based on the outcome, the majority of patients recovered, and only a few died because of drug-induced liver injury. This was compared with the results of a study conducted by Chalasani et al. (2015) In their study, 10% of patients died or underwent liver transplantation and 17% had chronic liver injury with DILI.[14] Also, Chalasani N et al. (2008) reported that 14% of patients had persistent laboratory abnormalities and 8% had died, the cause of death was liver-related in 44% of patients in their study.[16]

CONCLUSION

In conclusion, complementary and alternative medicine and antitubercular therapy were identified as the most common causes of drug-induced liver injury. CAMS is associated with significant morbidity and mortality. Additionally, the intake of CAMS in individuals with underlying CLD led to the deterioration of liver function, with patients progressing from Child-Turcotte-Pugh stage B to more severe CTP stage C. These findings highlight the critical need for caution when using CAMS, especially in patients with pre-existing liver conditions, to prevent the worsening of hepatic outcomes.

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