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ORIGINAL ARTICLE

Steroid-responsive intractable pruritus in drug-induced liver injury: a case series

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ABSTRACT

Background: Drug-induced liver injury (DILI) is commonly caused by modern medications, complementary and alternative medicines (CAMs), and other toxins. DILI is an umbrella term encompassing herb-induced liver injury (HILI) caused by herbs and CAMs, in addition to other medications. Apart from the cessation of the culprit drug and the supportive management, there are no definite treatment options for DILI. Although being used in DILI, steroids are not the standard medications for DILI, except that they are indicated for a few specific conditions.
Materials and Methods: We report five cases of DILI with pruritus who responded well to steroids used as rescue therapy. DILI in these five cases was caused by CAMs (1), anabolic steroids (2), dapsone (1), and antifungal drug itraconazole (1). All patients presented with jaundice and pruritus, and their conditions did not improve following the discontinuation of offending agents and the implementation of supportive care. We used the Roussel UCLAF Causality Assessment Method 2016 for causality assessment. R-value was used to describe the pattern of liver injury. All patients underwent comprehensive work-up including liver biopsy as part of the procedure to rule out other potential etiologies. Steroids were used as a last resort, and both clinical and biochemical measurements were conducted.
Results: The mean age of patients was 28.8 years, and the majority of them were males (80%). The median duration from symptom onset to presentation at our hospital was 4 weeks. The mean durations for pruritus improvement and complete biochemical improvement after steroid treatment were 3.2 weeks and 11.2 weeks, respectively. Extended follow-up was done for a mean period of 29.6 weeks from symptom presentation, and none of the patients had recurrence of liver injury after discontinuation of steroids.
Conclusions: Ssteroids can be used to treat as rescue therapy for severe DILI with intractable pruritus in patients with worsening liver function.
Relevance for Patients: DILI in selected cases can be therapeutically managed using steroids, which, however, should not be indicated as a first-line treatment.

1. Introduction

Drug-induced liver injury (DILI) is commonly caused by modern medications, complementary and alternative medicines (CAMs), and other toxins. DILI is an umbrella term encompassing herb-induced liver injury (HILI) resulted from herbs, CAMs, and other medications. DILI is divided into intrinsic (dose-dependent) and idiosyncratic (dose-independent) injuries [1]. Liver injury may be characterized as cholestatic, hepatocellular, or mixed injury, according to the results of liver function tests (LFT) and the calculation of the R-value. DILI may resemble liver diseases, particularly auto-immune hepatitis (AIH),

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making the diagnostic procedure challenging and necessitating differential diagnosis to rule out other liver diseases. In India, the combination of anti-tuberculosis (TB) drugs (46.4%), CAMs (13.9%), anti-epileptic drugs (8.1%), non-anti-TB antimicrobials (6.5%), anti-metabolites (3.8%), anti-retroviral drugs (3.5%), non-steroidal anti-inflammatory drugs (2.6%), hormones (2.5%), and statins (1.4%) represents the most common cause of DILI [2]. Management of DILI includes discontinuation of the culprit drug and administration of supportive care. However, in many patients, long after discontinuation of the culprit drug and implementation of supportive care, the injury fails to improve and progresses instead. Unfortunately, definitive management for such patients has not been developed. The role of steroids in the management of patients with DILI, except for those with immune checkpoint inhibitors [3] and drug-induced auto-immune hepatitis [4], remains doubtful. In other forms of DILI, the therapeutic effect of steroids has not been proven, especially when the injury is accompanied by pruritus. In the present study, we assessed the role of corticosteroids in five patients with DILI induced by different medications who had intractable pruritus and did not respond to conventional management.

2. Materials and Methods

Five patients were recruited in the Department of Gastroenterology, Banaras Hindu University, Varanasi, Uttar Pradesh, India, from January 2022 to December 2022. Patients were diagnosed with DILI secondary to CAMs (1), anabolic steroids (2), dapsone (1), and itraconazole (1). All these patients failed not respond adequately to the discontinuation of the offending agents and the supportive care and their condition even exacerbated. This case series depicts the etiology, clinical profile, management, and outcomes of patients with DILI and HILI. The R-value was calculated to define the patterns of liver injury. R-value was calculated by dividing alanine aminotransferase (ALT) by alkaline phosphatase (ALP), using multiples of the upper limit of normal (ULN) for both. R-value of >5 defines hepatocellular; <2, cholestatic; and between 2 and 5, a mixed pattern of liver injury. Patients were thoroughly evaluated to identify the alternative causes of liver injury, such as hepatotropic viruses, autoimmune liver diseases, Wilson's disease, and biliary obstruction by imaging. A liver biopsy was performed in all cases for histopathological examinations. We used the updated (2016) version of the Roussel UCLAF Causality Assessment Method (RUCAM) for causality assessment [5] (Table 1). For cases of non-response or worsening of liver injury and pruritus despite discontinuation of the offending agents, both corticosteroids and supportive care were administered to the patients. Prednisolone was started either at a dose of 40 mg/day (cases 1, 2a, and 3) or 1 mg/kg/day (cases 2b and 4) depending on the choice of treating hepatologist. Patients were followed to observe the outcomes in terms of improvement in pruritus, normalization of liver enzymes, intolerance or adverse effects of corticosteroids, and recurrence of liver injury. Informed consent was obtained from all patients or their nearest kin. This work is reported as per the CARE guidelines.

3. Results and Case Descriptions

3.1. Results

The mean age of the enrolled patients was 28.8 years, and the majority were males (80%). The median duration from the onset of symptoms to the presentation at our hospital was approximately 4 weeks. Case 1 had polycystic ovarian disease for which she took CAMs, and Case 3 took dapsone for leprosy. Cases 2a, 2b, and 4 had no underlying comorbidities. RUCAM scores were 5 for Case 1, 7 for case 2b, and 6 for each of the other three patients. R-values were 4.0, 3.6, 7.0, 2.4, and 2.5 for Cases 1, 2a, 2b, 3, and 4, respectively. Although these patients had severe DILI, none had acute liver failure. Mean durations for pruritus improvement and complete biochemical improvement after steroid treatment were 3.2 weeks and 11.2 weeks, respectively. All patients had good tolerance with corticosteroids without presenting any conspicuous side effects. Extended follow-up was done for a mean duration of 29.6 weeks from the presentation, and none of the patients had recurrence of liver injury after discontinuation of steroids (Table 2). Figure 1 depicts values of bilirubin, ALP, and ALT at different time points in all cases.

3.2. Case descriptions

3.2.1. Case 1 - CAM-induced liver injury with intractable pruritus in the background of doubtful choledocholithiasis

A 26-year-old female patient complained of abdominal pain, jaundice, and itching all over the body for 6 months before seeking medical consultation in our hospital. Her symptoms worsened at night, severely diminishing quality of sleep and life. On general examination, she had excoriating maculopapular skin lesions all over the body, with a few lesions showing oozing of blood (Figure 2A). Two weeks before presentation to our hospital, she underwent endoscopic retrograde cholangiopancreatography (ERCP) for biliary stone extraction and biliary stenting at another hospital. Her symptoms worsened, and she was admitted to our hospital and thoroughly investigated (Table 3). The biliary system was not dilated on imaging post-ERCP. Because there was no definitive diagnosis, a liver biopsy was performed. The results unveiled portal tract neutrophilic and eosinophilic infiltrates with hepatocellular and canalicular cholestasis with cholestatic rosettes predominantly in zone 3, suggesting mixed hepatocellular and cholestatic pathology (Figure 3, Case 1); DILI was considered a probable diagnosis. On re-inquiring, she admitted to having consumed CAMs for polycystic ovarian disease, which she started a few weeks before the onset of jaundice and stopped 15 days before presentation at our hospital. Her RUCAM score was five points, which suggests a possible DILI/HILI. The patient was given ursodeoxycholic acid (UDCA) 10 mg/kg/day. For treating pruritus, she received topical emollients, anti-histaminic, cholestyramine, and naltrexone; however, these medications were not therapeutically effective as her symptoms persisted during her hospital stay. She was started on prednisolone 40 mg/day which was slowly tapered later as her pruritus, jaundice, and skin lesions improved drastically at 3 weeks of follow-up (Figure 2B). Over

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Table 1. Detailed causality assessment in all patients using updated RUCAM# 2016 [5]

Updated RUCAM parameters	Case 1	Case 2a	Case 2b*	Case 3	Case 4
Time to onset from the beginning of the drug/herb consumption	+2	+2	+2	+2	+2
Course of ALP/ALT* after cessation of the drug/herb (percentage difference between ALP/ALT* peak and normal)	+1	+1	+2	+1	+1
Risk factors	0	0	0	0	0
Concomitant use of drugs/herbs	0	0	0	0	0
Search for alternative cause	+1	+1	+1	+1	+1
Previous hepatotoxicity of the drug/herb	+1	+2	+2	+2	+2
Response to unintentional re-exposure	0	0	0	0	0
Total score	5	6	7	6	6

#RUCAM score and causality grading: ≤0, excluded; 1–2, unlikely; 3–5, possible; 6–8, probable; ≥9, highly probable.
*Hepatocellular pattern of liver injury

Table 2. Duration of important events in all patients

Events	Case 1	Case 2a	Case 2b	Case 3	Case 4
Time to onset from the beginning of the drug/herb consumption (weeks)	3	10	8	6	Few weeks
Duration of from symptoms onset to presentation at our hospital (weeks)	24	4	3	6	3
Clinical (pruritus) improvement (weeks)	3	3	4	2	4
Biochemical improvement (normalization of LFT) (weeks)	11	11	14	8	12
Total follow-up duration without recurrence (data collected through phone call) (weeks)	36	32	24	28	28

Abbreviation: LFT: Liver function test.

the next 11 weeks, prednisolone was tapered and stopped with normalization of LFT parameters and resolution of pruritus. The patient was further followed for approximately 36 weeks, during which she did not manifest any symptoms and her liver enzyme levels were normal.

3.2.2. Case 2 - Anabolic steroid-induced liver injury

(A) Patient 2a

A 26-year-old male patient, who is a bodybuilder, presented with worsening jaundice, severe itching, malaise, and abdominal discomfort for 1 month. He had no comorbidities. His itching was more pronounced at night, disrupting his sleep. He had been taking stanozolol 50 mg intramuscularly on alternate days for 3 months to improve his physique. He discontinued the drug after the onset of symptoms. On physical examination, he had a body mass index of 27.6 kg/m^2, icterus, and hepatomegaly of 4 cm below the right costal margin. At admission, the patient's total bilirubin (TB) was 31.6 mg/dL. Other biochemical and serological parameters are illustrated in Table 3. Result from magnetic resonance cholangiography was normal. Despite the positive Kayser-Fleischer (KF) ring, his 24-h urinary copper and serum ceruloplasmin levels were normal. His RUCAM score was seven points. Examination of percutaneous liver biopsy showed that his liver had preserved architecture with portal tracts showing mild mixed inflammation, characterized by lymphomononuclear cells with a fair number of neutrophils and a mild ductular reaction. Hepatocytes showed intracellular and canalicular cholestasis predominantly in zone 3. Canalicular bile plugs, cholestatic rosettes, and prominent zone 3 perivenulitis were also noted. These findings were suggestive of mixed hepatocellular-cholestatic pathology compatible with DILI (Figure 3, Case 2a). The patient received UDCA, silymarin, anti-histaminic, and cholestyramine for several days, but his pruritus worsened and bilirubin rose to 42.2 mg/dL. The international normalized ratio (INR) increased to 1.6 from a baseline of 1. The patient was started on oral prednisolone 40 mg/day and naltrexone for severe pruritus. Over 3 weeks of follow-up, his pruritus and jaundice improved. The results of LFT are as follows: TB – 10.6 mg/dL, direct bilirubin (DB) – 6.8 mL/dL, aspartate aminotransferase (AST) – 45 IU/L, ALT – 68 IU/L, ALP – 90 IU/L, gamma-glutamyl transpeptidase (GGTP) – 40 IU/L, and INR – 1.1. The steroid was slowly tapered and discontinued over the next 8 weeks of follow-up when his liver function parameters became normal. He was followed for the next 21 weeks after stopping steroid therapy and was doing well.

(B) Patient 2b

A 24-year-old male, a gym enthusiast without any comorbidities approached us with worsening jaundice and severe itching, which had persisted for 20 days. He had been taking creatine and some steroid tablets for performance enhancement for 2 months and stopped after the onset of symptoms. The patient could not provide the exact details of the pills he was taking. TB and DB were 22.3 and 16.8 mg/dL, respectively, during presentation at our hospital. Other biochemical and serological parameters are summarized in Table 3. His RUCAM score was 7 points, suggesting a probable DILI. His R-value was seven, suggesting a hepatocellular pattern of liver injury. Histopathologically, his liver demonstrated a normal architecture, accompanied by few enlarged hepatocytes with mild intrahepatic and canalicular cholestasis, and lobular lymphocytic infiltrates with few eosinophils. Mild interface hepatitis was seen. Eosinophilic cholangitis with moderate chronic inflammatory cell infiltrate of the portal tract was also noted. Overall, these features were suggestive of cholestatic

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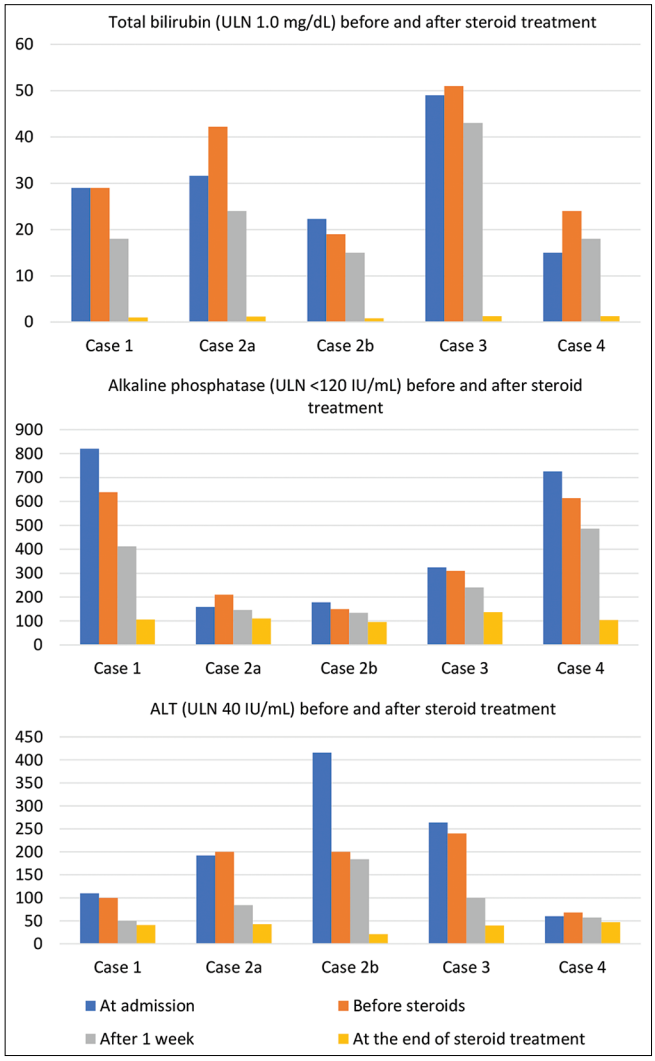

Figure 1. Total bilirubin, alkaline phosphatase, and alanine aminotransferase levels at different time points in all five patients.

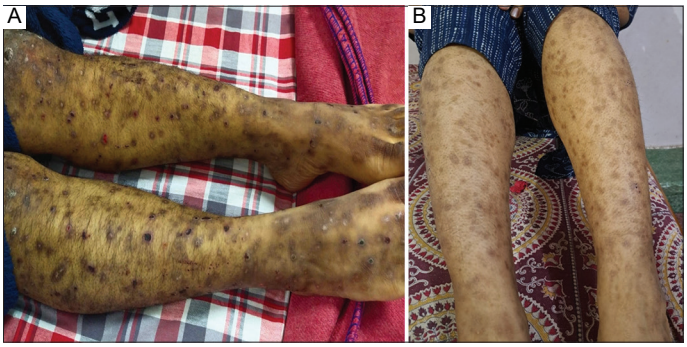

Figure 2. Skin lesions in Case 1 before (A) and after steroid therapy (B).

hepatitis with mild portal fibrosis and eosinophilic infiltrates with the possibility of DILI (Figure 3, Case 2b). He was given UDCA and anti-histaminic. However, since these medications were not effective, oral prednisolone (1 mg/kg/day) was administered. Over the next 4 weeks, his pruritus improved, and TB decreased to 7.3 mg/dL (direct – 5.8 mL/dL), ALT – 88 IU/L, AST – 65 IU/L, ALP – 104 IU/L, and GGTP – 92 IU/L. Prednisolone was tapered over the next 10 weeks and stopped after complete normalization of liver function. He was further followed for 10 weeks after steroid discontinuation, during which recurrence did not occur.

3.2.3. Case 3 - Dapsone-induced liver injury

A 52-year-old male patient presented with worsening jaundice and pruritus for the 1.5 months before seeking medical consultation at our hospital. He had been taking dapsone 100 mg daily as anti-leprosy treatment in the past 3 months. He was not taking any other medications, was a non-addict, and had no comorbidities, except leprosy. On physical examination, madarosis, contracture of upper limb fingers, and large hypopigmented hypoesthetic patches at the trunk and back were present. Features of hypersensitivity were absent. He had deep icterus but there were no clinical signs of liver failure. TB and DB were 49 and 40 mg/dL, respectively. KF rings were present in both eyes, and 24-h urinary copper was slightly elevated (Table 3). Serum ceruloplasmin was normal. His RUCAM score was 6 points, and his R-value was 2.4, suggesting a mixed pattern of DILI. Based on these results, dapsone was discontinued, and a liver biopsy was performed, demonstrating prominent acinar disarray, mild-to-moderate inflammatory infiltrates in the portal tract, and ductular reactions with focal neutrophilic cholangitis. Giant hepatocytes, zone 3 canalicular and intrahepatic cholestasis, and prominent zone 3 perivenulitis were also noted. Copper staining was negative. The overall picture suggested mixed hepatitis and cholestatic pattern, which was possibly drug-induced (Figure 3, Case 3). Emollients, anti-histaminic, and UDCA were given but liver functions continued to worsen, and oral prednisolone (40 mg/day) was started as rescue therapy. At 2 weeks of follow-up, his TB was 8.3 mg/dL (direct – 6.6 mL/dL). Other liver function parameters were ALT – 65 IU/L, AST – 98 IU/L, ALP – 154 IU/L, and GGTP – 171 IU/L. The patient's liver function parameters became normal after 8 weeks of treatment. Afterward, the patient was referred for further management of leprosy with special advice to avoid dapsone. Up to 18 weeks after steroid discontinuation, the patient did not report any signs of recurrence.

3.2.4. Case 4 - Antifungal-induced liver injury

Case 4 is a 16-year-old adolescent who had been taking itraconazole for Tinea corporis infection prescribed by a local physician, which he inadvertently continued for a prolonged period (several weeks). Following this, he developed jaundice, pruritus, and night blindness over approximately 3 weeks. Symptoms were worse at night, markedly hampering his quality of life. For these symptoms, he took some CAMs for the past 10 days, which were not clinically beneficial. Physical findings included exfoliated skin with intense scratch marks all over the body, deep icterus, Bitot's spots, and ecchymotic patches. TB and DB were 15 and 10 mg/dL, respectively, at presentation (Table 3). Although KF ring was bilaterally positive, 24-h urinary copper and serum ceruloplasmin were normal. His RUCAM score was 6 points, and his R-value was 2.4, indicating a mixed pattern of DILI. He had severe cholestasis

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Table 3. Summary of laboratory parameters of all patients during presentation at our hospital

Parameters	Case 1	Case 2a	Case 2b	Case 3	Case 4
Implicated drug	CAM	Anabolic steroid	Anabolic steroid	Dapsone/Rifampicin	Itraconazole
Age (years)	26	26	24	52	16
Gender	Female	Male	Male	Male	Male
BMI (18.5–23.5 kg/m^2)	24.5	27.6	25	20	16
Hemoglobin (12.5–15.5 g/dL)	12.7	15	14.6	13.9	11
TLC (4500–10,000/mm^3)	11000	8100	7200	6100	4500
Platelet count (1.5–4.5 L/mm^3)	2.9 L	3.5 L	2.8 L	2.6 L	1.8 L
ALT/AST/ALP (<40/<40/<120 IU/L)	110/96/820	192/107/159	416/187/178	264/272/324	60/112/725
GGT (<40 IU/L)	280	92	259	168	320
TB/DB (0.3–1.0/0–0.3 mg/dL)	29/21	31.6/22.3	22.3/16.8	49/40	15/10
Protein/albumin (6.0–8.3/3.5–5.0 g/dL)	6.9/3.9	6.5/4.3	7.1/4.6	6.5/4.1	6.0/4
PT/INR (<1.5)	16/1.2	14/1.0	14.3/1.1	13.9/0.9	74/7.7
Creatinine (0.2–1.0 mg/dL)	0.8	1.0	0.9	0.7	0.5
HBsAg/Anti-HCV	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR
IgM Anti-HAV/HEV/HBc	NR/NR/NR	NR/NR/NR	NR/NR/NR	NR/NR/NR	NR/NR/NR
Autoimmune profile (ANA, ASMA, anti-LKM 1, anti-SLA, AMA-M2)	Negative	Negative	Negative	Negative	Negative
Total IgG (1200 –1600 mg/dL)	1180	1400	1250	1360	1150
Ceruloplasmin (20–60 mg/dL)	29	30	21	28	23
24-h urinary copper (<60 µg/day)	45	38	25	60	55
KF ring	Negative	Positive	Negative	Positive	Positive
R-value	4.0	3.6	7.0	2.4	2.5

Abbreviations: BMI: Body mass index; HCV: Hepatitis C virus; HAV: Hepatitis A virus; HEV: Hepatitis E virus; NR: Non-reactive; SLA: Soluble liver antigen; ANA: Anti-nuclear antibody; AMA: Anti-mitochondrial antibody; LKM: Liver kidney microsome; ASMA: Anti-smooth muscle antibody; IgG: Immunoglobulin G; KF: Kayser-Fleischer

as indicated by severe pruritus and fat-soluble vitamin deficiencies (Vitamin A and Vitamin K). As the patient had severe coagulopathy at presentation (prothrombin time – 74; and INR – 7.7), a trans-jugular liver biopsy was performed. Histopathological examination unveiled marked acinar disarray with areas of lobular inflammatory cell infiltrates and zone 3 cholestasis. Portal tracts showed mild lymphomononuclear inflammation with few admixed neutrophils and eosinophils. Hepatocytes showed focal ballooning degeneration, and canalicular cholestasis with cholestatic rosettes in zone 3. These findings suggested mixed hepatitis and cholestatic pathology compatible with DILI (Figure 3, Case 4). He was given UDCA, an anti-histaminic, and fat-soluble vitamin supplements. Despite all these measures, his pruritus and liver biochemical parameters did not improved and instead became worse. Hence, oral prednisolone (1 mg/kg/day) was prescribed. At 4 weeks of steroids administration, his pruritus and jaundice improved, and the stigmata of fat-soluble vitamin deficiencies disappeared. LFT results of this patient are as follows: TB – 2.3 mg/dL (direct – 1.5 mL/dL), ALT – 70 IU/L, AST – 54 IU/L, ALP – 150 IU/L, GGTP – 86 IU/L, and INR 1.2. Prednisolone was slowly tapered over 8 weeks, and his clinical and liver parameters became normalized. He was followed for the next 16 weeks after discontinuation of steroid therapy, during which recurrence of symptoms did not occur.

4. Discussion

Drugs, herbs, toxins, and CAMs are common causes of liver injury and are commonly seen in hepatology practice. In India, where medications can easily be obtained over the counter, it is not surprising to encounter cases afflicted with classical forms of DILIs, such as the case presenting itraconazole-induced hepatotoxicity described in this paper. Pruritus is a common symptom of cholestatic liver injury resulting from medications, and its treatment is often complex and difficult to achieve curative effect. Several agents are available for treating pruritus in different patterns of liver injury; however, the efficacy of these agents varies without any firm recommendations.

CAMs account for 14% of total DILI cases in Indian Network for DILI (INDILI) [2]. These drugs usually contain unknown constituents—possibly heavy metals—making it difficult to identify the culprit agent [6]. One Indian study reported that 6.5% of liver disease patients who presented to the outpatient and emergency departments had ayurvedic and herbal medicine-related severe DILI and one-third of these patients ingested them for gastrointestinal symptoms [7]. According to the U.S. Drug-induced Liver Injury Network (DILIN), dietary supplements were the causative agents in 16% of cases [8]. Multiple studies confirmed that anabolic steroid use can cause hepatotoxicity, such as cholestasis, steatohepatitis, peliosis hepatis, and hepatic tumors [9]. Dapsone is known to cause drug hypersensitivity syndromes (DHS), such as drug reaction with eosinophilia and systemic symptoms (DRESS) and DILI. DILI in these cases may be hepatocellular, cholestatic, or mixed, and is usually associated with hypersensitivity. A mixed pattern is the most common type of hepatotoxicity resulting from dapsone [10]. DILI induced by antifungal drugs such as azoles and echinocandin is one of the

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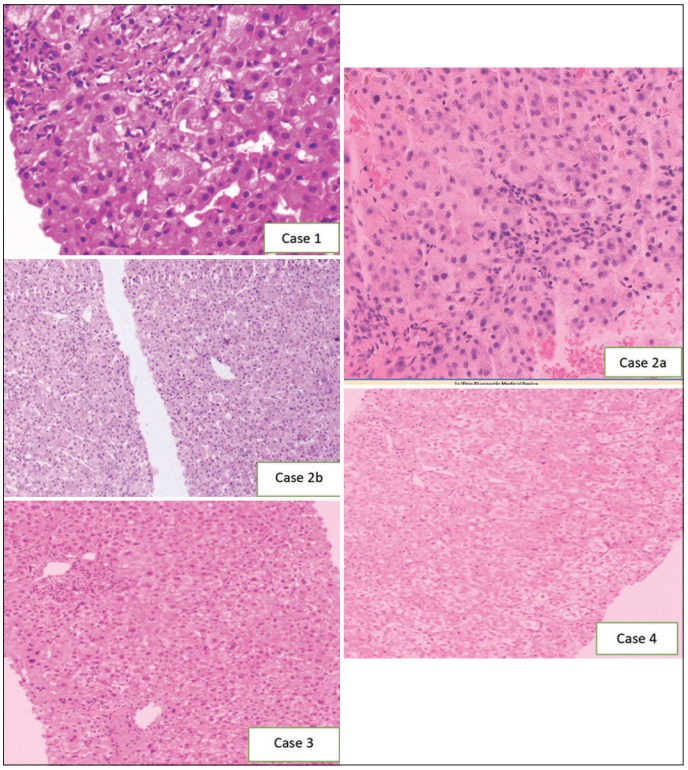

Figure 3. Histopathological micrographs of the liver (hematoxylin and eosin staining) of all patients.

most common adverse events [11] and contributes to 2.9% of all cases of DILI [12].

Identification and discontinuation of the culprit agents and avoidance of re-exposure are the mainstays of DILI management. In most patients, spontaneous recovery occurs after the culprit drug is discontinued [13]. DILI, in its natural course, may develop acute or sub-acute liver failure and may prove fatal if liver transplantation is not implemented [14]. Pruritus hampers the quality of life to a great extent, and in severe cases, patients may develop suicidal tendencies. For severe pruritus, drugs like antihistaminics, namely, hydroxyzine or diphenhydramine, topical emollients, and soothing agents like lactocalamine can be attempted. Cholestyramine provides symptomatic relief in patients with pruritus.

At present, there is no specific therapy for changing the natural course of DILI [15,16]. Steroids have been recommended in patients with drug-induced autoimmune hepatitis, DILI secondary to immune checkpoint inhibitors and biologicals, and DILI with features of hypersensitivity [17,18]. The role of steroids in other causes of DILI has been studied with mixed results presented in uncontrolled studies. A retrospective study showed that 15 patients treated with a combination of prednisolone and ursodeoxycholic acid exhibited a rapid reduction in bilirubin, liver enzymes, and INR [19]. Another retrospective study with a larger number of patients described a beneficial effect of corticosteroid therapy in terms of mortality benefit and rapid recovery in severe DILI [20]. In addition, budesonide has been reported to be beneficial in two patients without autoimmune features [21]. Contrary to these findings, two studies reported that corticosteroid administration was not found to be beneficial, but instead, was harmful to patients with severe DILI [22] and DILI-related acute liver failure [23]. A recent report from prospective DILI registries concluded that corticosteroid therapy did not worsen outcomes in DILI patients, and its administration led to a greater rate of normalization of liver enzymes in patients with severe DILI [24]. Amidst these mixed results on the role of corticosteroids in DILI/HILI, a recent open-label randomized controlled study concluded that steroids may accelerate the recovery of patients with severe DILI [25].

Despite a very limited number of patients, the present study demonstrates the beneficial role of corticosteroids in the treatment of DILI. In the present study, four patients had mixed patterns of liver injury with predominant cholestasis, leading to severe pruritus that significantly hampered quality of life in three patients (cases 1, 2a, and 4). The severity of pruritus in Case 1 was characterized by intense itching, which led to skin excoriations and bleeding. Case 2b had a hepatocellular pattern of liver injury (R-value = 7) with cholestatic symptoms, which can be explained by cholestatic pattern of liver injury by histopathologic means. Most patients with DILI recovered following the cessation of culprit agents, without showing signs of progression. Typically, patients with progressive liver injury may have severe DILI or end up with liver failure, in which secondary infections play a major role, and may face a very high mortality risk if liver transplantation is not implemented. Treatment with steroids in the setting of liver failure may increase the risk of secondary infections, posing a negative impact on the overall outcome. None of our patients had features of liver failure. Severe coagulopathy in Case 4 due to itraconazole-induced DILI can be explained by cholestasis leading to Vitamin K malabsorption. This patient had features of fat-soluble Vitamin A deficiency; therefore, he responded well to Vitamin A supplements in addition to corticosteroids.

Discontinuation of culprit medications along with supportive management was not sufficient to keep the patient's liver parameters and symptoms under control. Thus, steroids were prescribed as a rescue therapy for the patients, and all of them responded well to steroids without exhibiting any adverse effects. The beneficial effects of steroids in DILI may be attributed to its anti-inflammatory action. However, therapeutic effect of steroids in pruritus is conditional on the improvement in liver function and cholestasis. In the present study, improvement in pruritus was observed in a mean duration of 3.2 weeks and complete normalization of LFTs was achieved in a mean period of 11.2 weeks.

Several limitations of this study should be acknowledged. A small number of patients and the absence of a control group are significant limitations of this study, which prevent us from drawing a firm conclusion about the role of steroids in such scenarios. Furthermore, we did not perform tests for atypical viruses like herpes simplex virus, Epstein bar virus, varicella-zoster virus, and cytomegalovirus that can cause liver injury. Three patients had KF ring, as confirmed during slit lamp examination, but a genetic analysis for the *ATP7B* gene was not performed to completely rule out Wilson's disease in these cases.

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5. Conclusions

A short course (a few weeks) of steroids can be used to effectively treat DILI and intractable pruritus in patients without liver failure. However, large prospective controlled studies are needed to confirm the role of corticosteroids in these situations.

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None.

Conflicts of Interest

The authors declare no conflicts of interest.

Ethics Approval and Consent to Participate

As this study was retrospective in nature, research ethics approval was not obtained. However, written informed consent was obtained from all patients for inclusion in the study.

Consent for Publication

Written informed consent was obtained from all patients for using their data in a publication.

Availability of data

Data are available from the corresponding author on reasonable request.

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